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February 12, 2002  
Ref: TCW-020190

8EHQ-0202-15078

via Federal Express

MR 55403

Attn.: TSCA Section 8(e) Coordinator  
**U.S. ENVIRONMENTAL PROTECTION AGENCY**  
Ariel Rios Building  
1200 Pennsylvania AVE  
Washington, DC 20460



8EHQ-02-15078

Re: **28 Day Repeated Oral Toxicity Test**

Dear Sir or Madam:

In accordance with the reporting requirements of TSCA Section 8(e), **Clariant Corporation** hereby submits the results of "28 Day Repeated Oral Toxicity Tests of V4221 in Rats" on a Substituted imidoalkylcarboxylic acid known as V4221.

The results of this test indicate that the NOEL of the substance is 40 mg/kg/day. The discussion in the abstract of the general state of the animals is stated as

"during the period of administration, salivation was seen in males and females in groups given 200 mg/kg and higher, decrease in spontaneous movement and decrease in respiratory rate were seen in males in the 200 mg/kg group, decrease in spontaneous movement, decrease in respiratory rate, soiling around the nose and mouth, hunchback posture, soiling around anus and loss of hair from the mandible were seen in males and females in the 1000 mg/kg group and soft stool, reddish tears, reddish tear traces and ptosis were seen in males in the 1000 mg/kg group."

Although there may be some markings on the test as included, we are not claiming this information as Confidential Business Information in this specific notification.

The test substance is currently undergoing evaluation through our Research and Development process and is not commercially available.

If any further information is required, please contact me as show above.

Best regards,

Contain NO CBI

*Carole M. Dixon*

Carole M. Dixon, Director  
Corporate Product Safety

CMD/tcw

Enclosure



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Acceptance No. [ D94-1427 ]  
Report No. [ D-4288 ]

Test Code No. [ B11-0301 ]

## FINAL REPORT

28 Day Repeated Oral Toxicity Tests of [ V4221 ] in Rats

November 1995

[ Kagakuin Kensa Kyokai [Chemical Products Testing Association], Inc.  
Hita Research Laboratories, Chemical Products Safety Center  
(Seal) ]

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Statement

[Chemical Products Testing Association, Inc.  
Hita Research Laboratories, Chemical Products Safety Center]

Test consignor:

[Hoechst Industries Company, Ltd.]

Title of test:

28 Day Repeated Oral Toxicity Tests of [V4221] in Rats

Test Code No.:

[B11-0301]

The aforementioned tests were executed in accordance with "Test Facilities as Stipulated in Article 4 of the Directive Setting Items for Tests New Chemical Substances and Studies of Harmfulness of Specified Chemical Substances" based on Environmental Protection Affairs Directive No. 39, Drug Issue Directive No. 229, Basic [Research] Bureau No. 85-1984 of March 31, 1984 and Environmental Affairs Directive No. 233, Hygiene Directive No. 38 and Basic [Research] Bureau No. 1988-823 of November 18, 1988) and with "OECD Principles of Good Laboratory Practice" (May 12, 1981).

November 6, 1995

Operations Manager: [illegible] Yamane [seal affixed]

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## Reliability Assurance Report

[Chemical Products Testing Association, Inc.  
Hita Research Laboratories, Chemical Products Safety Center]

Test consignor:

[Hoechst Industries Company, Ltd.]

Title of test:

28 Day Repeated Oral Toxicity Tests of [V4221] in Rats

Test Code No.:

[B11-0301]

The QA Office of the [Hita Research Laboratories, Chemical Products Safety Center] performed monitoring and inspection of these tests. The dates on which the monitoring or inspection was performed and the dates on which reports were made by the operations manager and test supervisor are indicated below.

Date of monitoring or inspection	Report dates (Operations manager)	Report dates (Test supervisor)
May 8, 1995	May 8, 1995	May 8, 1995
June 27, 1995	June 28, 1995	June 28, 1995
July 3, 1995	July 4, 1995	July 4, 1995
July 5, 1995	July 7, 1995	July 7, 1995
July 21, 1995	July 24, 1995	July 24, 1995
August 1, 1995	August 3, 1995	August 4, 1995
August 10, 1995	August 10, 1995	August 10, 1995
August 14, 1995	August 21, 1995	August 21, 1995
August 17, 1995	August 21, 1995	August 21, 1995
October 5, 1995	October 5, 1995	October 5, 1995
October 5, 1995	October 18, 1995	October 18, 1995
October 23, 1995	October 25, 1995	October 25, 1995
November 6, 1995	November 6, 1995	November 6, 1995

This is to certify that the methods and procedures used in the tests are accurately recorded in this report and that the report results accurately reflect the raw data.

November 6, 1995

Reliability Assurance Department Supervisor [Keiji Shiraishi [seal affixed]]

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[B11-0301]

Test Code No.: [B11-0301]  
Test Substance Code No.: [HR2928]  
Consignor Code No.: [H-010]

Title: 28 Day Repeated Oral Toxicity Tests of [v4221] in Rats

Test Consignor: [Hoechst Industries Company, Ltd., 10-16 Asasaka 8-chome,  
Minato-ku, Tokyo-to]

Test Facility: [Hita Research Laboratories, Chemical Products Safety  
Center, Chemical Products Testing Association, Inc.  
822 Ishii-machi 3-chome, Hita-shi, Oita-ken, 877]

Test Objective:  
The objective was to clarify the type, degree and reversibility and the no observed effect level (NOEL) of the toxicity syndrome that appears by observing changes in function and morphology in the body when the test substance was administered orally for 28 days to animals.

Test Method:  
The tests were conducted in accordance with "28 Day Repeated Toxicity Tests Using Mammals" as stipulated in "Partial Revision of 'Methods of Testing New Chemical Substances'" (Environmental Protection Affairs Directive No. 700, Drug Issue Directive No. 229 and Basic [Research] Bureau Directive No. 1014-1986 of December 5, 1986) and in "407. Repeated Dose Oral Toxicity - Rodent: 28-Day or 14-Day Study" (May 12, 1981) as stipulated in "OECD Guidelines for Testing of Chemicals."

Applicable GLP:  
"Test Facilities as Stipulated in Article 4 of the Directive Setting Items for Tests of New Chemical Substances and Studies of Harmfulness of Specified Chemical Substances" (Environmental Protection Affairs Directive No. 39, Drug Issue Directive No. 229, Basic [Research] Bureau Directive No. 85-1984 of March 31, 1984 and Environmental Research Directive No. 233, Hygiene Directive No. 38 and Basic [Research] Bureau Directive No. 823-1988 of November 18, 1988) and "OECD Principles of Good Laboratory Practice" (May 12, 1981) were used.

Test Periods

Date test was begun: May 8, 1995

Date animals were acquired: June 27, 1995

Date administration was begun: July 4, 1995

Autopsy date after administration period was completed:  
August 1, 1995

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Date recovery period began:	August 1, 1995
Autopsy date after recovery period was completed:	August 15, 1995
Date tests were concluded:	November 6, 1995

#### Data Storage Site and Period of Storage

The data and specimens relating to the tests are to be stored in the Data Storage Room of the Hita Research Laboratories of this association and samples of each lot of the test substance are to be stored in the Test Substance Storage room for a period of 10 years from the date completion of the test. Disposition after the storage period requires approval of the test consignor. However, the storage period for moist specimens that undergo marked changes in quality during storage is set as a period during which the quality is tolerable for evaluation. The approval of the test consignor is to be obtained for their discard.

#### Preparer of final report and test participants

##### Signature and seal of preparer of final report

Test Supervisor: November 6, 1995  
[Takaaki Umano [seal affixed]]  
Affiliation: [Test Research Section 5, Hita Research Laboratories]

Pathological Analysis Supervisor: November 6, 1995  
[Saneharu Yamazaki [seal affixed]]

Clinical Test Supervisor: November 6, 1995  
[Keiji Shiraishi] [seal affixed]

#### Test Participants

Test Supervisor: [Takayuki Koga]

Work Assignment Supervisor: [Teruhiko Kanebayashi]  
(Specialist in Toxicological Pathology authorized by the Japanese  
Toxicological Pathology Society. Affiliation: Biopathology Research  
Laboratories Company, Inc.)

Analysis Supervisor: [Ritsuko Yoshida]

#### Circumstances that were not anticipated and departures from the test protocol

There were no circumstances that were not anticipated and there were no departures from the test protocol that had deleterious effects on the reliability of the test.

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[B11-0301]

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Test Report

CC0262

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### Abstract

28 day repeated oral toxicity tests and 14 day repeated tests of [V4221] were performed using 5 week old male and female Crj:CD(SD) rats with 6 animals per group. Four doses were set, 1000 mg/kg as the high dose and 200, 40 and 8 mg/kg. Recovery groups were established for the 1000 and 200 mg/kg groups and the solvent control group.

No deaths due to administration of the test substance were seen in these tests.

No effects due to administration of the test substance were seen on body weight and feed consumption during the period of administration or on the urinalyses at the time administration was concluded.

In terms of general states, during the period of administration, salivation was seen in males and females in groups given 200 mg/kg and higher, decrease in spontaneous movement and decrease in respiratory rate were seen in males in the 200 mg/kg group, decrease in spontaneous movement, decrease in respiratory rate, soiling around the nose and mouth, hunchback posture, soiling around anus and loss of hair from the mandible were seen in males and females in the 1000 mg/kg group and soft stool, reddish tears, reddish tear traces and ptosis were seen in males in the 1000 mg/kg group.

In the hematological tests, at the time administration was concluded, increase in leukocyte counts was seen in males in groups given 200 mg/kg and higher, decreases in hemoglobin concentrations and hematocrit values were seen in males and females in the 1000 mg/kg, decrease in erythrocyte counts and increase in the ratio of rod neutrophils were seen in males in the 1000 mg/kg group and delay in activated partial thromboplastin time and a tendency toward decrease in erythrocyte counts were seen in females in the 1000 mg/kg group.

In the blood biochemistry tests, at the time administration was concluded, decrease in blood sugar was seen in males in groups given 100 mg/kg and higher, decrease in chlorine was seen in females in groups given 200 mg/kg or higher, increase in total bilirubin was seen in males in the 1000 mg/kg group and increase in triglycerides and decrease in creatinine were seen in females in the 1000 mg/kg group.

In the study of organ weights, at the time administration was concluded, increases in liver weights were seen in females in groups given 200 mg/kg and higher and in males in the 1000 mg/kg group.

On autopsy, at the time administration was concluded, apparent surface spotting of the kidneys and roughening of the mucosa of the glandular stomach were seen in males in the 1000 mg/kg group.

In the histopathological tests, at the time administration was concluded, increase in eosinophilic bodies in the liver was seen in males in groups given 200 mg/kg or higher, enlargement of liver cells was seen in males and females in the 1000 mg/kg group and granulation tissue accompanied by calcification and mucosal degeneration of the proventriculus [forestomach] were seen in males in the 1000 mg/kg group.

In the recovery tests, soiling around the anus was seen in males and females in the 1000 mg/kg group following the administration period but disappeared by the time the recovery period was concluded. In tests at the time the recovery period was concluded, decreases were seen in hemoglobin concentrations and erythrocyte counts in females in the 1000 mg/kg group, increases in total bilirubin was seen in males in groups given 200 mg/kg and higher, increase in liver weight was seen in males and females in the 1000 mg/kg group and increase in liver weight, decrease in testis weight and increase in eosinophilic bodies in the liver were seen in males in the 1000 mg/kg group.

On the basis of the foregoing results, the NOEL of [V4221] in rats under the conditions of this test was presumed to be 40 mg/kg/day.

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## Experimental Materials and Experimental Methods

## 1 Test substance and positive control substance

## 1.1 Designation

[Reaction product of propylene polymer, maleic anhydride addition product and  $\epsilon$ -caprolactam]

Alternate name: [V4221]

CAS No.: ----

## 1.2 Lot No.

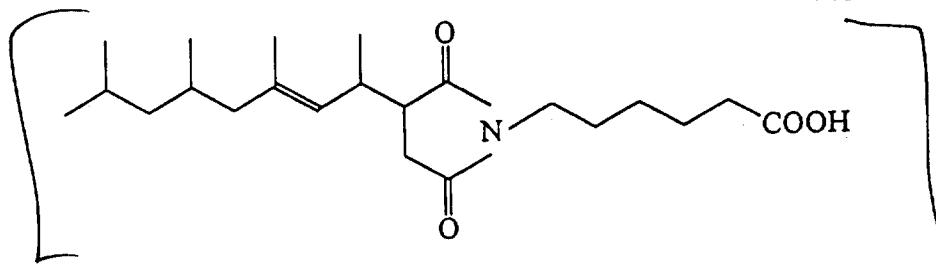
[o.p. 2/94]

## 1.3 Source

[Hoechst Industries Company, Ltd.]

## 1.4 Structural formula and rational formula (synopsis of manufacturing method when either not clear)

Representative structural formula



(molecular formula (representative) [C<sub>22</sub>H<sub>37</sub>NO<sub>4</sub>])

## 1.5 Purity

100%

## 1.6 Designations and concentrations of impurities

-----

## 1.7 Physical and chemical properties

Properties at normal temperature  
Brown viscous liquid

Molecular weight (representative)

[379.54]

Stability

Stable

Melting point  
-20 to -30°C

Boiling point  
185°C

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Vapor pressure  
-----

Partition coefficient  
-----

Solubility (25°C)

Water: Because the test substance was distributed and solubility differed, determination was not possible.

DMSO: -----

Acetone: -----

Other

Hexane: 14 g/liter

Chloroform: over 100 g/liter (visual observation)

Ethyl acetate: over 100 g/liter (by HPLC determination)

Methanol: over 100 g/liter (visual observation)

#### 1.8 Storage conditions

It was stored in a cold, dark place.

#### 1.9 Cautions on handling

Gloves, masks, caps and white clothing were worn.

### 2. Animals used

Crj:CD(SD) rats (SPF) that were produced by the Japan Charles River Company, Ltd. (Hino Rearing Center, 735 Shimokamozuki, Hino-machi, Gamo-gun, Shiga-ken, 529-16) were purchased. After they had been quarantined and acclimatized, animals in good general condition and that had grown smoothly were assigned to groups by the body weight random stratified sampling method so that the average body weights in each group were essentially equal. At the time administration was begun, the animals were 15 weeks old. The body weight ranges were 122.6 to 142.0 g in males and 100.9 to 118.3 g in females. The animals were identified by ear punches.

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### 3. Rearing environment

During the period of execution of the test, the animals were reared individually in cages with stainless steel wire net flooring (165 W x 300 D x 150 H mm; [Tokiwa Kagaku Kikai Company, Ltd.]) in a barrier system rearing room at a temperature of  $23 \pm 2^{\circ}\text{C}$ , a relative humidity of  $55 \pm 10\%$  and a ventilation frequency of 10 to 15 times/hour in which the light and darkness cycle was set at 13 hour intervals (illumination turned on at 0700 hours and extinguished at 1900 hours). The trays were changed twice a week, the cages once a week and the racks once in two weeks. Labels were attached to the racks and cages for identification. The animals were given free access to solid feed [MF, Oriental Yeast Industrial Co., Ltd.] and drinking water from the Hita City tap water (chlorinated) by means of an automatic water dispenser. The feed and the containers for the feed were sterilized in an autoclave for 30 minutes at  $121^{\circ}\text{C}$ . A mixture of the feed and drinking water was analyzed and it was confirmed that they could not impair the test.

During the quarantine and acclimation periods and during the test period, no fluctuations that could have affected the results of the tests were found in these feed environment factors.

### 4. Group composition

The group composition was set as shown in the following table.

Test Group	Dose (mg/kg/ day)	Dose Vol. (ml/kg)	Dose Concen. (%)	Number of Animals	
				Males (animal no.)	Females (animal no.)
Solvent control group	0	10	0	6 ( 1- 6)	6 (49-54)
Solvent control recovery group	0	10	0	6 ( 7-12)	6 (55-60)
Low dose group	8	10	0.08	6 (13-18)	6 (61-66)
Medium dose (1) group	40	10	0.4	6 (19-24)	6 (67-72)
Medium dose (2) group	200	10	2	6 (25-30)	6 (73-78)
Medium dose (2) recovery group	200	10	2	6 (31-36)	6 (79-84)
High dose group	1,000	10	10	6 (37-42)	6 (85-90)
High dose recovery group	1,000	10	10	6 (43-48)	6 (91-96)

#### Reasons for setting doses:

14-day repeated preliminary tests were performed using three doses, 60, 250 and 1000 mg/kg. As a result, abnormalities were seen in the hematological tests, the blood biochemistry tests and autopsies in the 1000 mg/kg group, in organ weights in the 250 mg/kg group and in the general state in the 50 mg/kg group. Consequently, four dose levels were set in this test, 1000 mg/kg as the high dose, followed by 200, 40 and 8 mg/kg. In the recovery group, 1000 and 200 mg/kg groups and a solvent recovery group were established.

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5. Preparation of test substance

5.1 Preparation methods

- 1) Carboxymethyl cellulose sodium (CMC, [Lot No. WDF0723, Wako Junyaku Kogyo Company, Ltd.] that has been precisely weighed out was added to purified water ([Takasugi Seiyaku Company, Ltd.]) and was dissolved by stirring to make a 0.5% CMC aqueous solution (10 w/v% used at time of preparation).
- 2) CMC and polyoxyethylene (20) sorbitan monooleate (Tween 80, [Lot No. KCM2063, Wako Junyaku Kogyo Company, Ltd.] that had been precisely weighed out was added to purified water and was dissolved by stirring to make an 0.5% CMC aqueous solution containing 3% Tween 80 (2, 0.4 and 0.08 w/v% diluted preparations prepared at the time of use).
- 3) The test substance and Tween 80 (3% concentration relative to the final solution volume) were precisely weighed out and were kneaded and suspended as 0.5% CMC aqueous solution and was added continuously in small quantities to give a 10 w/v% concentration. Dilute preparations were made using 0.5 CMC aqueous solution containing 3% Tween 80 from the 10 w/v% concentration to give 2, 0.4 and 0.08 w/v% concentrations. These preparations were made once a week.

5.2 Stability and homogeneity tests

Stability tests and homogeneity tests of the test substance prepared by this method were performed by this association and it was confirmed that it was stable and homogeneous.

6. Administration

A Nelaton's catheter ([Thermo Company, Ltd.]) was connected to a syringe ([Thermo Company, Ltd.]) and the preparations were given by forced oral administration for 28 days every morning. A subsequent 14 day recovery period was established.

7. Observation and examination

In calculating the starting day and week, the day administration was begun was taken as day 1, the day before administration was taken as day -1 and the week administration was begun was taken as week 1. The day following the day administration was concluded was taken as day 1 (recovery) and the week recovery was begun was taken as week 1 (recovery).

7.1 Observation of general states of animals

In all cases, observations were made one or more times a day.

7.2 Determination of body weights

In all cases, determinations were made on day -2 before administration (when group assignments were made), days 1 (administration), 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26 and 28 during the administration period and on days 1 (recovery) 3, 5, 8, 10, 12 and 14 during the recovery period.

In order to calculate relative organ weights, determinations were made once immediately before autopsy.

7.3 Determination of feed consumption

In all cases, determinations were made once before administration and two times a week during the administration and recovery periods.

## 7.4 Hematological tests

In all cases, blood was drawn from the abdominal aorta under ether anesthesia when the administration period was concluded and when the recovery period was concluded after one night of fasting (16 to 20 hours). Sodium citrate was used as an anticoagulant in testing prothrombin time and activated thromboplastin time. EDTA-2K was used in the other tests. The test items indicated below were performed on the blood and plasma that were obtained.

Item		Method
1) Erythrocyte count (RBC)	( $\times 10^4/\text{mm}^3$ )	Electric resistance detection method
2) Leukocyte count (WBC)	( $\times 10^2/\text{mm}^3$ )	Electric resistance detection method
3) Hemoglobin concentration (Hb)	(g/dl)	Oxyhemoglobin method
4) Hematocrit value (Ht)	(%)	Pulse detection method
5) Mean corpuscular volume (MCV)	( $\mu\text{m}^3$ )	Ht ----- $\times 10^3$ RBC
6) Mean corpuscular hemoglobin (MCH)	(pg)	Hb ----- $\times 10^3$ RBC
7) Mean corpuscular hemoglobin concentration (MCHC)	(%)	Hb ----- $\times 10^2$ Ht
8) Platelet count	( $\times 10^4/\text{mm}^3$ )	Electric resistance detection method
9) Reticulocyte count ratio (Reticulo)	( $\text{o}/\text{oo}$ )	New methylene blue staining
10) Prothrombin time (PT)	(sec)	Magnetic sensor system
11) Activated partial thromboplastin time (APTT)	(sec)	Magnetic sensor system
12) Differential leukocyte count (Differentiation of leukocyte) (%)		Rod neutrophils (N-Band) Segmented neutrophils (N-Seg) Eosinophils (Eosino) Basophils (Baso) Lymphocyte (Lymph) Monocytes (Mono)

## Equipment used:

- 1)-8) Automatic blood cell counter (Microcell counter M-2000, [Toa Iyo Denshi])
- 9), 12) Automatic blood cell analyzer (MICROX HEG-120A, [Omron])
- 10), 11) Automatic blood coagulation determination apparatus (KC-10A, [Amelung])

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### 7.5 Blood biochemistry tests

At the time of the blood biochemistry tests, serum was separated from the collected blood and the test items indicated below were performed on the serum that was obtained.

Item		Method
1) GOT	(IU/l)	UV method (JSCC conforming formulation)
2) GPT	(IU/l)	UV method (JSCC conforming formulation)
3) Alkaline phosphatase (ALP)	(IU/l)	p-nitrophenyl phosphate method
4) Cholinesterase (ChE)	(IU/l)	butyrylthiocholine iodide method
5) $\gamma$ -GTP	(IU/l)	L- $\gamma$ -glutamyl-p-nitroanilide method
6) Total cholesterol (T-Chol)	(mg/dl)	COD-SAOD method
7) Triglycerides (TG)	(mg/dl)	GPD-DAOS method
8) Blood glucose (glucose)	(mg/dl)	glucokinase-G-6-PDH method
9) Total protein (T-protein)	(g/dl)	Biuret method
10) Albumin (Albumin)	(g/dl)	bromocresol green method
11) A/G ratio (A/G ratio)		albumin ----- (calculated value) T-protein - albumin
12) Urine nitrogen (BUN)	(mg/dl)	urease indophenol method
13) Creatinine (Creatinine)	(mg/dl)	Jaffe method
14) Total bilirubin (T-Bil)	(mg/dl)	Azo bilirubin method
15) Calcium (Ca)	(mg/dl)	OCPC method
16) Inorganic phosphorus (IP)	(mg/dl)	Fiske-Subbarow method
17) Sodium (Na)	(mEq/l)	Crown-ether membrane electrode method
18) Potassium (K)	(mEq/l)	Crown-ether membrane electrode method
19) Chlorine (Cl)	(mEq/l)	Coulometric titration method

#### Equipment used:

- 1) - 10, 120 - 16): Automatic biochemical analyzer (7150 Automatic Analyzer, Hitachi)  
 17) - 19): Electrolyte analyzer (PVA- $\alpha$  III, A & T)

### 7.6 Urinalysis

In all cases, urinalyses were performed once during the administration period (day 28) and once during the recovery period (day 14 (recovery)).

16-hour urine that was collected in individual metabolic cages was examined for urine volume and color tone and tests of pH, protein, ketone bodies, bilirubin, occult blood, sugar and urobilinogen were performed using test paper (N-Multisticks [phonetic] \* (R), [Miles-Sankyo]).

\* Translator's Note: Transliterated from the [Japanese]. As such, the spelling may differ from other transliterations.

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7.7 Autopsies

Detailed observations were made in all cases.

7.8 Organ weight determinations

Wet weights of the following organs were determined in all cases.  
Brain, liver, spleen, kidney, adrenals, testes (or ovaries)

7.9 Histopathological tests

- 1) In all cases, the following organs and tissues were fixed in formalin.

Brain (cerebrum, cerebellum), pituitary, eyeballs, thyroid (including epithelial bodies), heart, lungs, liver, kidneys, spleen, adrenals, stomach, intestines (duodenum - rectum), testes (or ovaries), bladder, bone marrow (femur), regions of macroscopic pathological change

- 2) The organs and tissues in the groups indicated below were embedded in paraffin and sectioned, after which they were stained with hematoxylin-eosin stain and were studied under the optical microscope. An assignment protocol was prepared for specimen preparation and the studies under the optical microscope, which were performed by the Biopathology Laboratories Company, Ltd. (1200-2 Owara, Kunisaki-machi, Higashikunisaki-gun, Oita-ken 873-05). In preparing the final report, overall analyses and evaluations of histopathology were made by the pathology supervisor of this association on the basis of the assigned operations report.

Test period

Solvent control group, 100 mg/kg group: Liver, spleen, kidneys, heart, stomach, intestines (duodenum, jejunum, ileum, cecum, colon, rectum), testes, adrenals

200 mg/kg group: Liver, kidneys (males only), stomach (males only), testes

40 mg/kg group: Liver (females only), kidneys (males only)

8 mg/kg group: Kidneys (males only)

Recovery period

Solvent control group, 1000 mg/kg group: Liver, kidneys (males only), stomach (males only), testes

200 mg/kg group: Liver, kidneys (males only) testes

Sites of macroscopic pathological changes

Administration period

Male, 1,000 mg/kg group (No. 39): Skin

Recovery period

Male, 200 mg/kg group (No. 33): Glandular stomach

Female, 200 mg/kg group (No. 80): kidneys

Fat staining (Oil red O stain) of the liver was performed in the solvent control group (No. 51) and the 1,000 mg/kg group (No. 87).

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8. Statistical methods

The findings for body weight, feed consumption, hematological tests, blood biochemistry tests, urine volume and organ weights were subjected to homoscedastic analysis by Bartlett's test. When equal variance at a 5% level of significance was found, tests between the solvent control group and each administration group were performed by Dunnett's method when the number of cases in each group were equal and by Scheffe's method when they were not equal.

When equal variance was not found, the Kruskall-Wallis test was performed. When significant differences were found, tests between the solvent control group and each administration group were performed by Dunnet's method when the number of cases in each group was equal and by Scheffe's nonparametric method when they were not equal.

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## 9.2 When the recovery period was concluded

Males: Increase in eosinophilic bodies (+, 1/6) in the liver was seen in the 1000 mg/kg group. In addition, microgranuloma in the liver ( $\pm$ , 3/6; +, 2/6) and cyst formation in the kidneys (1/6) were seen in the solvent control group, microgranuloma and ( $\pm$ , 3/6; +, 1/6) perilobular lipid droplets ( $\pm$ , 1/6) in the liver, dilatation of the renal pelvis (1/6) and necrosis of the mucosa of the glandular stomach (+, 1/1) were seen in the 200 mg/kg group and microgranuloma ( $\pm$ , 3/6; +, 1/6) in the liver was seen in the 1000 mg/kg group.

Females: Microgranuloma of the liver ( $\pm$ , 2/6; +, 3/6) and perilobular lipid droplets ( $\pm$ , 2/6; +, 1/6) were seen in the solvent control group, microgranuloma of the liver ( $\pm$ , 4/6), perilobular lipid droplets ( $\pm$ , 2/6; +, 2/6), dilatation of the renal pelvis (1/1) and pyelonephritis (++, 1/1) were seen in the 200 mg/kg group and microgranuloma of the liver ( $\pm$ , 3/6; +, 3/6) and perilobular lipid droplets ( $\pm$ , 2/6; +, 1/6) were seen in the 1000 mg/kg group.

## Discussion

[V4221] was given by forced oral administration to SD strain rats in doses of 8, 40, 200 and 1000 mg/kg/day and 28-day toxicity tests and 14-day recovery tests were performed.

In our current tests, no deaths due to administration of the test substance were seen.

No effects were seen by administration of the test substance on body weights and feed consumption during the administration period and in the urinalyses when the administration period was concluded.

Effects of administration of the test drug on the general state that were seen during the administration period were salivation in males and females in groups given 200 mg/kg and higher, decrease in spontaneous movement and decrease in respiratory rate in males in the 200 mg/kg group, decrease in spontaneous movement, decrease in respiratory rate, soiling around the nose and mouth, hunchback posture, soiling around the anus and depilation in the lower neck region in males and females in the 1000 mg/kg group and soft stool, reddish tears, reddish tear traces and ptosis in males in the 1000 mg/kg group. Although depilation in the neck region and scab formation, which were seen in the 1000 mg/kg group, were seen at a high frequency, they were also seen at low doses and it was concluded that they were attributable to retention at the time of administration.

In the hematological tests at the time the administration period was concluded, decrease in hemoglobin concentration and in hematocrit values were seen in males and females in the 1000 mg/kg group, decreases in erythrocyte counts were seen in males in the 1000 mg/kg group and prolongation of activated partial thromboplastin time and decreases in erythrocyte counts were seen in females in the 1000 mg/kg group. In addition, increases in leukocyte counts were seen in males in groups given 200 mg/kg and higher and increase in the rod neutrophil ratio was seen in males in the 1000 mg/kg group. It was concluded that these fluctuations were findings attributable to administration of the test substance.

In the blood biochemistry tests at the time the administration period was concluded, decrease in blood sugar was seen in males in groups given 200 mg/kg and higher, increase in total bilirubin was seen in males in the 1000 mg/kg group, decrease in chlorine was seen in females in groups given 200 mg/kg and higher and increase in triglycerides and decrease in creatinine were seen in females in the 1000 mg/kg group. It was concluded that these fluctuations were findings attributable to administration of the test substance.

In the study of organ weight, it was concluded that the increases in the liver weight that were seen in females in groups given 200 mg/kg and higher and in males in the 1000 mg/kg group at the time the administration period were findings attributable to administration of the test substance.

On the autopsies at the time administration was concluded, apparent surface spotting of the kidneys was seen in males in the 1000 mg/kg group. In addition, roughening of the mucosa of the glandular stomach was seen in 1 case in this same group. It was concluded that these findings were attributable to administration of the test substance. However, no findings correlated with the changes in the glandular mucosa were seen in the histopathological studies.

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In the histopathological studies at the time administration was concluded, increase in eosinophilic bodies in the kidneys were seen in males in the group given 200 mg/kg and higher, swelling of hepatocytes was seen in males and females in the 1000 mg/kg group, granulation tissue accompanied by calcification in the liver and mucosal degeneration of the proventriculus [forestomach] were seen in males in the 1000 mg/kg group. It was concluded that these findings were attributable to administration of the test substance.

The effects of administration of the test substance that were seen during the administration period or when the administration period was concluded in the recovery tests were as follows. Findings for general state included soiling around the anus, which was seen continuously in males and females in the 1000 mg/kg group during the administration period. However, it had disappeared by the time the recovery period was concluded. In the hematological tests, decrease of hemoglobin concentrations persisted and decrease in counts of new erythrocytes were seen in females in the 1000 mg/kg group. In the blood biochemistry tests, increase in total bilirubin persisted in males in the 1000 mg/kg group and increase in total bilirubin was seen in males in the 200 mg/kg group. In the studies of organ weights, increase of liver weight persisted in males and females in the 1000 mg/kg group and increase in liver weight and decrease in testis weight were seen in males in the 1000 mg/kg group. However, no histopathological abnormalities of the testes were seen. In the histopathological studies, increase in eosinophilic bodies in the kidneys persisted in 1 male in the 1000 mg/kg group. In addition, it was concluded that the new changes that were seen in the hematological studies and blood biochemistry studies were adventitious changes because similar changes were not seen at the time administration was concluded and no related findings were seen.

It was further concluded that findings and items for which significant differences were found that were seen in addition to those described above were not findings attributable to administration of the test substance because they were sporadic and not dose-dependent and because they were also seen sporadically in the solvent control group.

On the basis of the foregoing results, it can be concluded that the principal effects of [V2411] are on the liver in males and females and on the proventriculus and kidneys in males. On the basis of salivation, decrease in spontaneous movement, decrease in respiratory rate, increase in leukocyte counts, decrease in blood sugar, decrease in chlorine, increase in liver weight and increase in eosinophilic bodies in the liver attributable to administration of the test substance that were seen in the 200 mg/kg group, it was presumed that the NOEL of [V4221] in rats under the conditions of this test was 40 mg/kg/day.

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[B11-0301]

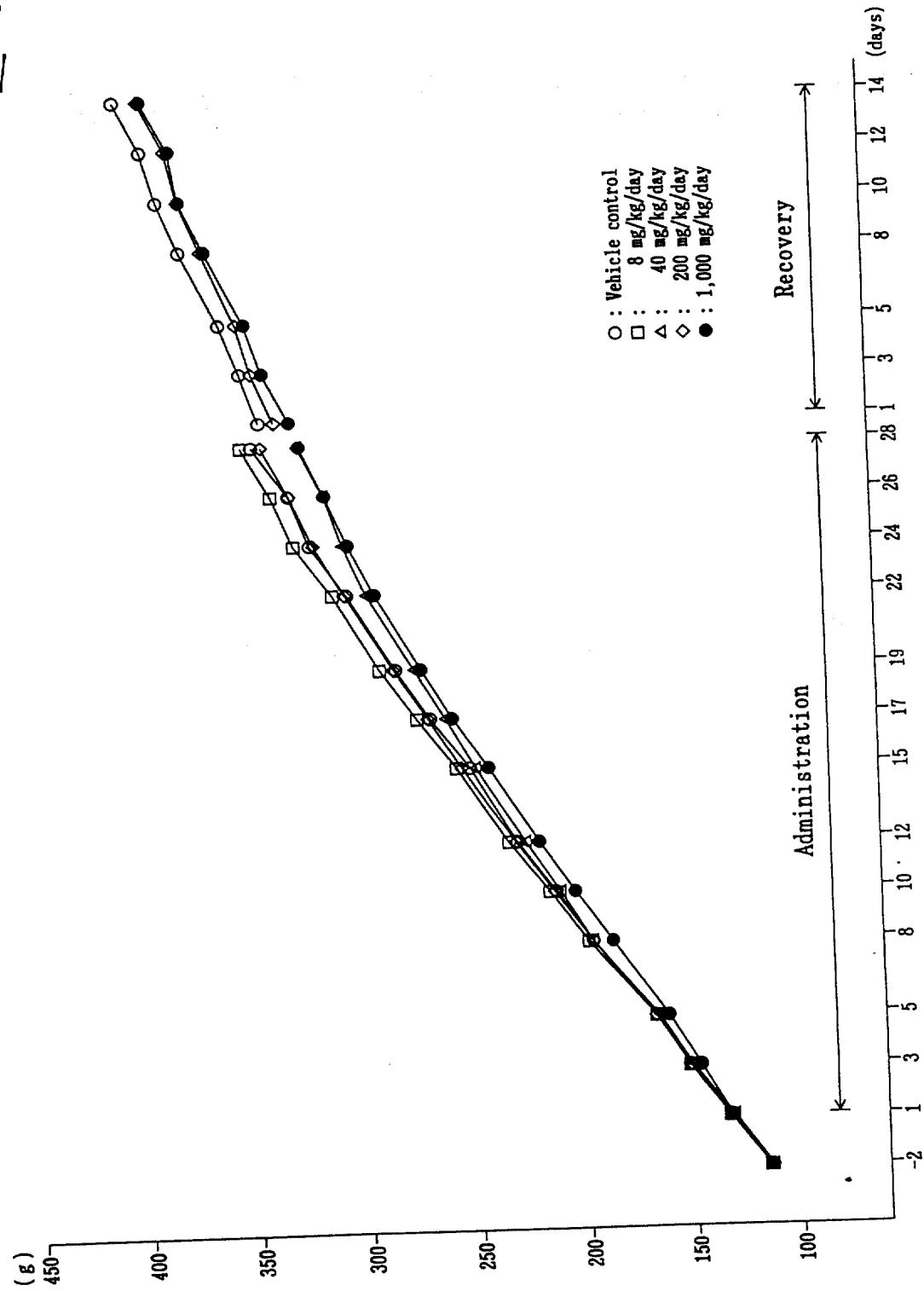
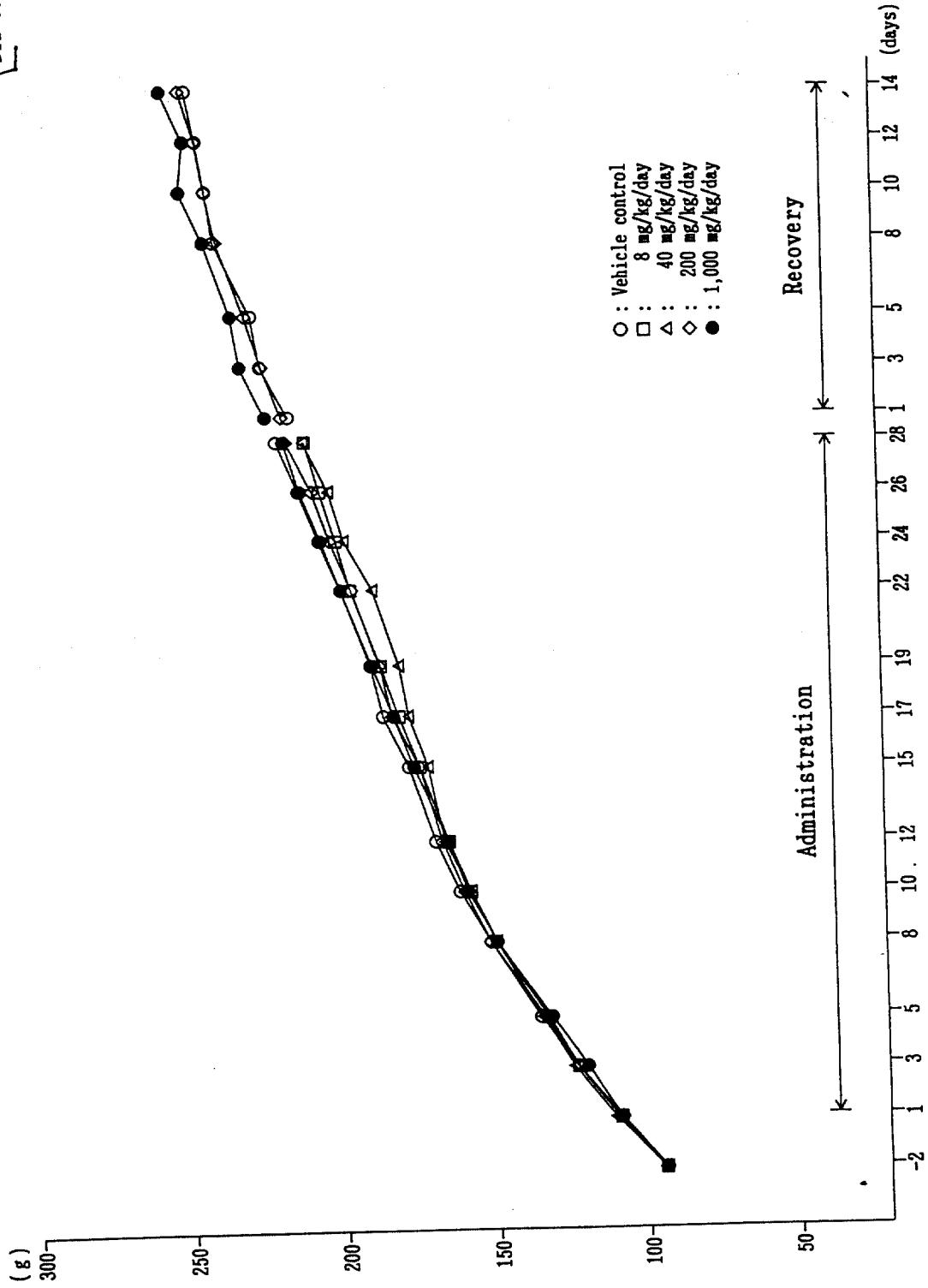


Figure 1 28-day repeated-dose oral toxicity study in rats  
Mean body weights : Male

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[B11-0301]



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[B11-0301]

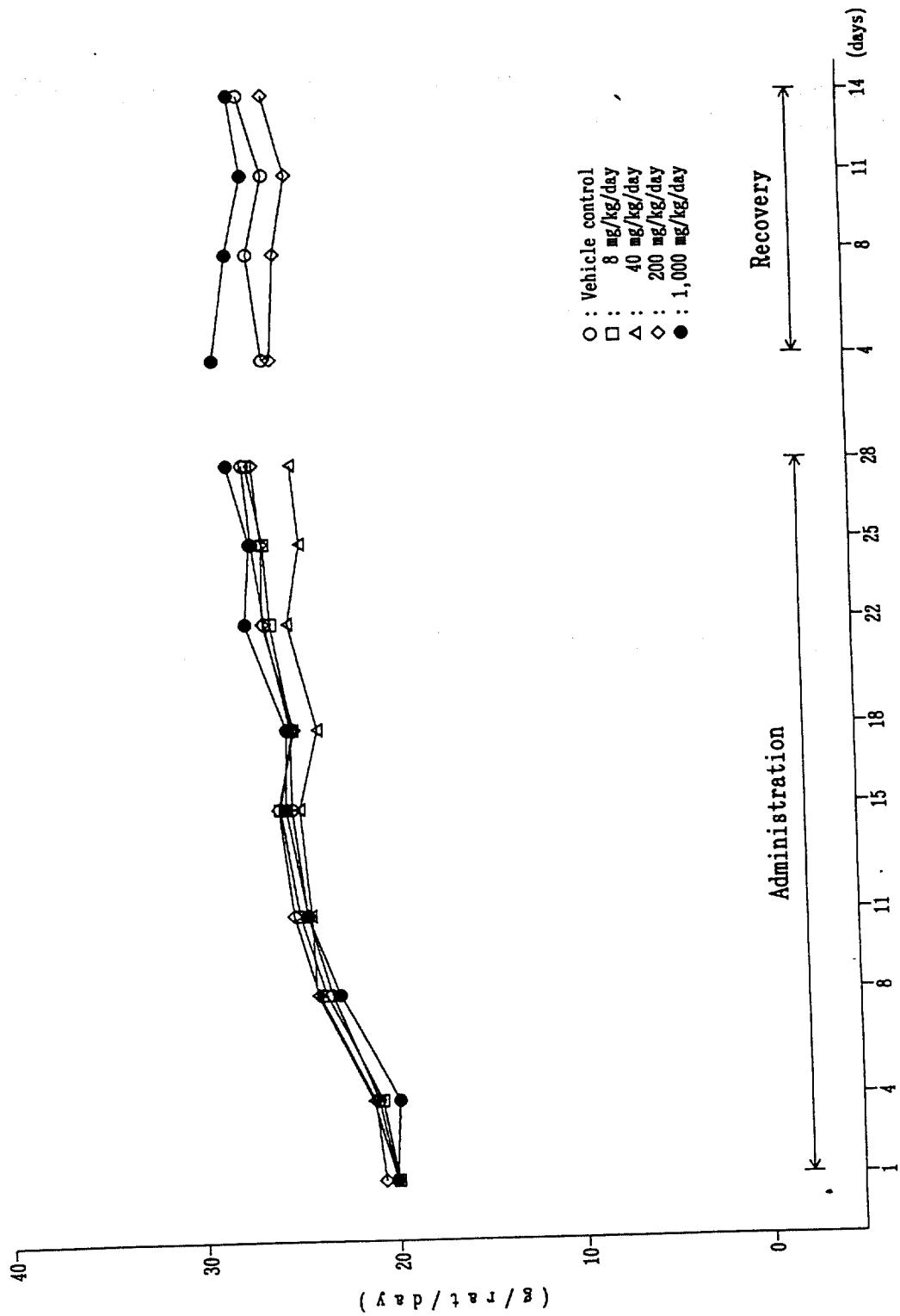


Figure 2 28-day repeated-dose oral toxicity study in rats  
Mean food consumption : Male

CC0280

[B11-0301]

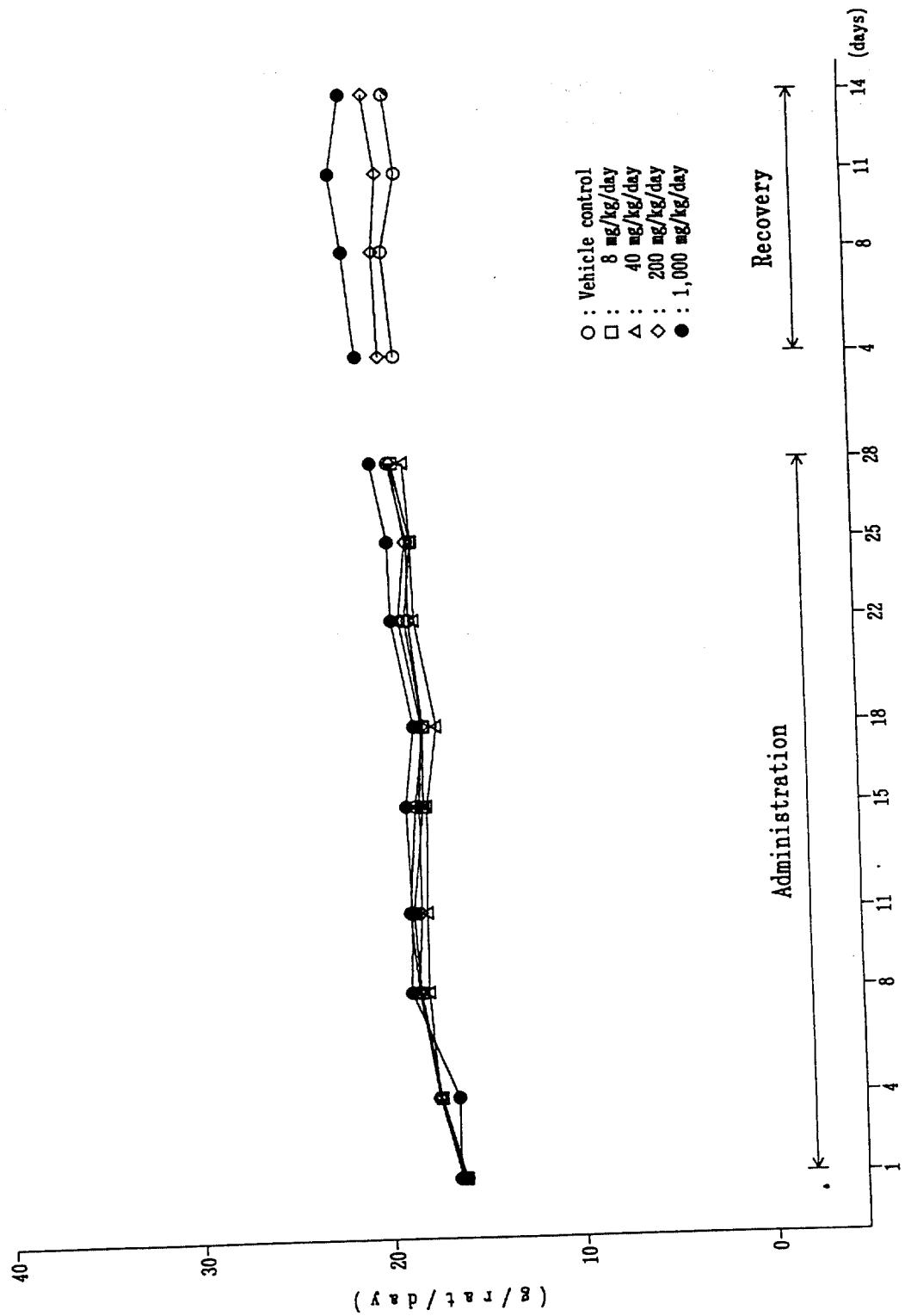


Figure 2 -Continued  
Mean food consumption : Female

CC0281

[B11-0301]

Table 1  
28-day repeated-dose oral toxicity study in rats  
Clinical signs

Sex	Signs	No. of animals (6 animals / group)												Recovery period	
		Administration period						Recovery							
		Vehicle control	Vehicle	40	200	200	1,000	1,000	1,000	control	200	1,000			
	No abnormalities detected	6	6	5	6	6	6	6	6	6	6	6	1		
	Salivation						6	4	6	6	6	6			
	Decreased spontaneous locomotion						2	5	5	5					
	Decreased respiratory rate						2								
	Soiled around nose and mouth						3	4							
	Soft stool						3	1							
	Hunchback						2	2							
	Male						2								
	Mark of reddish tear						1								
	Reddish tear						1								
	Petrosis						1								
	Soiled around anus						1	1							
	Loss of hair (mandible)						1	3							
	Loss of hair (neck)						1	4							
	Scab formation (neck)						1								
	No abnormalities detected	6	6	6	6	6	6	6	6	6	6	6	5		
	Salivation						6	6	6	6	6	6			
	Decreased spontaneous locomotion						4	5							
	Decreased respiratory rate						2	4							
	Female						3	3							
	Soiled around nose and mouth						2	1							
	Hunchback						1	2							
	Soiled around anus						2	1							
	Loss of hair (mandible)						1								

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[B11-0301]

Table 2 28-day repeated-dose oral toxicity study in rats  
Mean body weights(kg)

Sex	Exp.-group (mg/kg/day)	Number of animals	Administration					
			-2	1	3	5	8	10
Male	Vehicle control	12	114.0 ± 4.0	133.0 ± 4.5	152.0 ± 5.3	186.8 ± 7.0	195.6 ± 8.7	211.9 ± 11.3
	8	6	114.9 ± 4.6	133.7 ± 6.1	151.9 ± 7.0	187.2 ± 7.1	197.8 ± 7.5	215.0 ± 7.9
	40	6	113.5 ± 3.5	131.5 ± 4.5	150.4 ± 4.9	185.7 ± 6.9	195.7 ± 9.9	210.0 ± 8.6
Female	200	12	113.9 ± 3.8	133.0 ± 4.0	151.3 ± 4.9	187.4 ± 5.7	195.6 ± 7.6	213.0 ± 8.6
	1,000	12	114.6 ± 4.1	132.4 ± 4.6	146.5 ± 6.2	181.2 ± 7.2	188.4 ± 9.7	203.3 ± 9.5
	Vehicle control	12	94.5 ± 4.5	108.7 ± 5.4	123.3 ± 5.3	135.2 ± 5.7	151.5 ± 6.1	161.3 ± 6.2
N	8	6	94.5 ± 4.6	108.1 ± 5.2	123.2 ± 4.8	132.7 ± 5.3	149.7 ± 6.6	157.7 ± 5.7
	40	6	95.0 ± 5.3	110.8 ± 4.7	124.5 ± 6.8	134.6 ± 5.7	149.5 ± 8.5	157.6 ± 9.5
	200	12	94.7 ± 5.0	108.8 ± 5.6	123.2 ± 6.4	133.8 ± 6.7	151.6 ± 7.0	166.8 ± 8.2
D	1,000	12	94.4 ± 5.0	108.9 ± 5.8	119.9 ± 5.2	131.6 ± 7.8	149.4 ± 9.8	158.8 ± 10.2
	Vehicle control	12	94.5 ± 4.5	108.7 ± 5.4	123.3 ± 5.3	135.2 ± 5.7	151.5 ± 6.1	161.3 ± 6.2

Mean ± S.D.

\* : Significantly different from Vehicle control at P<0.05.  
\*\* : Significantly different from Vehicle control at P<0.01.

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Table 2 -Continued  
Mean body weights(g)

Sex	Exp group (mg/kg/day)	Number of animals	Administration					
			15	17	19	22	24	26
Male	Vehicle control	12	250.0	267.7	282.9	304.0	320.1	328.2
	8	6	256.2	273.9	290.1	310.4	327.5	337.2
	200	12	263.8	268.8	283.9	304.9	318.3	328.9
1,000	Vehicle control	12	241.5	257.6	271.1	291.4	302.7	312.8
	8	6	247.5	260.8	274.5	295.2	305.1	313.1
	200	12	241.5	257.6	271.1	291.4	302.7	312.8
Female	Vehicle control	12	177.5	185.7	189.5	198.9	205.9	212.4
	8	6	173.9	180.6	186.2	195.6	200.3	205.3
	200	12	174.0	182.6	186.5	195.4	202.2	207.8
3,000	Vehicle control	12	175.9	182.3	189.0	198.9	205.1	211.8
	8	6	171.1	177.2	180.1	188.4	197.6	202.4
	200	12	174.0	182.6	186.5	195.4	202.2	207.8

Mean  $\pm$  S.D.

\* : Significantly different from Vehicle control at P<0.05.  
\*\* : Significantly different from Vehicle control at P<0.01.

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Table 2 -Continued  
Mean body weights(g)

Sex	Exp. group (mg/kg/day)	Number of animals	Recovery					
			1	3	5	8	10	12
Male	Vehicle control	6	341.5 ± 20.0	349.5 ± 21.2	358.4 ± 21.0	375.7 ± 21.6	385.6 ± 23.3	392.6 ± 23.6
	200	6	334.6 ± 15.3	344.2 ± 16.4	350.7 ± 17.4	365.9 ± 17.9	375.8 ± 19.4	381.1 ± 18.0
	1,000	6	327.6 ± 19.6	339.3 ± 21.9	346.7 ± 21.7	364.2 ± 23.0	375.3 ± 24.2	383.4 ± 18.4
Female	Vehicle control	6	215.3 ± 17.0	224.1 ± 17.2	227.0 ± 16.7	239.1 ± 20.9	241.6 ± 17.3	244.4 ± 20.2
	200	6	217.5 ± 10.4	223.7 ± 14.5	229.2 ± 10.5	238.1 ± 16.0	241.8 ± 16.8	244.7 ± 14.8
	1,000	6	222.8 ± 18.4	230.8 ± 15.8	233.7 ± 17.7	242.5 ± 16.7	250.1 ± 16.0	248.5 ± 13.9

Mean ± S.D.

\* : Significantly different from Vehicle control at P<0.05.  
\*\* : Significantly different from Vehicle control at P<0.01.

C0285

Table 3 28-day repeated-dose oral toxicity study in rats  
Mean food consumption(g/rat/day)

Sex	Exp. Group (mg/kg/day)	Number of animals	Administration							
			1	4	8	11	15	18	22	25
Male	Vehicle control	12	20.1 ± 1.0	21.0 ± 1.3	23.3 ± 1.7	24.5 ± 1.8	25.2 ± 2.0	26.4 ± 2.3	27.0 ± 2.5	27.4 ± 2.6
	8	6	20.0 ± 1.1	20.8 ± 1.4	23.6 ± 0.8	24.9 ± 1.6	25.8 ± 1.1	26.1 ± 1.9	26.4 ± 1.7	27.2 ± 2.2
	40	6	20.1 ± 1.1	21.3 ± 1.1	24.1 ± 1.2	24.3 ± 0.9	24.8 ± 1.5	23.8 ± 1.4	25.2 ± 1.6	24.9 ± 1.2
Female	200	12	20.7 ± 1.1	21.2 ± 1.3	24.0 ± 1.4	25.2 ± 1.9	25.8 ± 1.6	26.0 ± 1.7	26.5 ± 1.8	26.9 ± 1.9
	1,000	12	20.1 ± 1.0	19.9 ± 1.4	22.9 ± 1.5	24.5 ± 1.7	25.5 ± 1.4	25.4 ± 1.2	27.1 ± 1.5	28.2 ± 1.7
	Vehicle control	12	16.4 ± 1.4	17.5 ± 1.1	18.4 ± 0.9	18.8 ± 0.9	18.4 ± 1.0	17.9 ± 1.1	18.5 ± 0.9	18.4 ± 1.0
Female	8	6	16.2 ± 0.5	17.4 ± 0.8	18.3 ± 0.5	18.6 ± 0.9	18.0 ± 0.7	17.9 ± 1.3	18.7 ± 1.3	19.2 ± 1.5
	40	6	16.3 ± 1.3	17.5 ± 1.1	17.9 ± 1.5	17.9 ± 1.7	17.8 ± 1.7	17.2 ± 1.8	18.3 ± 2.0	19.2 ± 1.9
	200	12	16.2 ± 1.4	17.5 ± 1.7	18.4 ± 1.2	18.2 ± 1.3	18.2 ± 1.3	18.0 ± 1.3	19.0 ± 1.2	19.3 ± 1.9
On	1,000	12	16.5 ± 1.3	16.5 ± 1.1	18.8 ± 1.2	18.7 ± 1.3	18.9 ± 1.6	19.4 ± 1.4	19.5 ± 1.5	20.3 ± 1.8

Mean ± S.D.

\* : Significantly different from Vehicle control at P<0.05.

\*\* : Significantly different from Vehicle control at P<0.01.

Table 3 -Continued  
Mean food consumption(g/rat/day)

Sex	Exp group (kg/kg/day)	Number of animals	Recovery				14 (days)
			4	8	11		
Male	Vehicle control	6	28.2	28.8	26.0	27.2	
	200	6	† 2.7	† 2.2	† 2.1	† 1.9	
	1,000	6	25.8	25.5	24.8	25.9	
Female	Vehicle control	6	28.8	28.0	27.1	27.7	
	200	6	† 1.8	† 1.4	† 1.7	† 1.7	
	1,000	6	† 1.5	† 1.7	† 1.2	† 1.8	

Mean ± S.D.

\* : Significantly different from Vehicle control at P<0.05.

\*\* : Significantly different from Vehicle control at P<0.01.

B11-0301

Table 4  
28-day repeated-dose oral toxicity study in rats  
Hematology

Sex	Exp.-group (mg/kg/day)	Number of animals	RBC (x10 <sup>6</sup> /mm <sup>3</sup> )	WBC (x10 <sup>3</sup> /mm <sup>3</sup> )	Hb (g/dl)	Ht (%)	HCV (μm <sup>3</sup> )	MCH (pg)	MCHC (%)	Platelet (x10 <sup>4</sup> /mm <sup>3</sup> )	Reticulo (%)	P T (sec)	APTT (sec)	
	Vehicle control	6	786 ± 14	74 ± 12	15.5 ± 0.6	44.5 ± 1.4	56.7 ± 1.6	19.7 ± 0.7	34.8 ± 0.6	121.6 ± 10.9	24 ± 9	16.6 ± 3.9	28.9 ± 3.1	
	8	6	780 ± 28	87 ± 18	15.3 ± 0.4	44.4 ± 1.6	56.9 ± 2.2	19.6 ± 0.6	34.4 ± 0.6	125.6 ± 11.7	19 ± 5	15.8 ± 2.2	30.1 ± 4.6	
	40	6	758 ± 24	74 ± 15	15.1 ± 0.5	43.6 ± 1.4	57.6 ± 1.4	19.9 ± 0.9	34.6 ± 0.4	121.5 ± 13.2	18 ± 6	16.0 ± 1.8	30.0 ± 2.5	
	200	6	751 ± 23	108** ± 13	15.0 ± 0.4	44.0 ± 1.0	58.7 ± 2.4	19.9 ± 0.5	34.0 ± 0.7	130.2 ± 15.6	24 ± 7	14.9 ± 2.1	30.7 ± 2.9	
Male	1,000	6	716** ± 38	107** ± 19	14.1** ± 0.4	41.2** ± 1.0	57.6 ± 2.2	19.8 ± 1.0	34.4 ± 0.9	136.4 ± 16.5	22 ± 6	17.8 ± 0.9	32.7 ± 3.3	
	Recovery Vehicle control	6	829 ± 47	117 ± 13	15.6 ± 0.5	45.0 ± 2.0	54.3 ± 2.5	18.8 ± 1.0	34.6 ± 0.7	115.5 ± 9.9	8 ± 4	14.1 ± 1.6	27.2 ± 3.8	
	200	6	809 ± 19	93 ± 20	15.2 ± 0.7	43.7 ± 1.6	54.0 ± 0.8	18.8 ± 0.4	34.9 ± 0.4	116.7 ± 10.4	9 ± 1	14.5 ± 2.1	24.1 ± 3.4	
	1,000	6	781 ± 42	112 ± 17	15.3 ± 0.3	44.1 ± 1.4	56.6 ± 2.7	19.6 ± 0.7	34.7 ± 0.8	110.6 ± 11.2	11 ± 5	15.7 ± 2.5	26.4 ± 1.9	
	Vehicle control	6	738 ± 22	71 ± 16	15.1 ± 0.6	42.1 ± 1.4	57.1 ± 2.0	20.5 ± 1.0	35.9 ± 0.9	129.1 ± 11.6	20 ± 8	12.0 ± 0.7	20.7 ± 0.8	
	8	6	755 ± 22	84 ± 20	15.3 ± 0.3	42.9 ± 1.6	56.8 ± 1.7	20.3 ± 1.7	35.8 ± 0.6	132.8 ± 7.2	12 ± 2	11.9 ± 0.6	21.9 ± 1.7	
	40	6	763 ± 16	83 ± 20	15.4 ± 0.4	43.1 ± 1.5	56.5 ± 1.6	20.2 ± 0.3	36.8 ± 0.7	125.5 ± 13.5	10* ± 2	11.9 ± 0.3	21.2 ± 1.5	
	200	6	731 ± 36	77 ± 10	14.8 ± 0.6	41.0 ± 2.5	56.1 ± 1.4	20.3 ± 0.5	36.2 ± 1.0	132.5 ± 16.7	14 ± 3	11.5 ± 0.5	22.1 ± 2.1	
	Female	1,000	8	707 ± 33	82 ± 21	13.9** ± 0.5	38.9* ± 1.5	55.1 ± 1.0	19.7 ± 0.6	35.7 ± 0.6	120.2 ± 6.3	20 ± 3	11.7 ± 0.9	25.9** ± 3.6
	Recovery Vehicle control	6	794 ± 24	75 ± 30	15.6 ± 0.4	43.3 ± 0.8	54.6 ± 1.4	19.7 ± 0.6	36.0 ± 0.8	120.6 ± 9.4	6 ± 5	11.3 ± 0.5	21.8 ± 2.3	
	200	6	772 ± 21	57 ± 8	15.1 ± 0.3	41.9 ± 0.8	54.4 ± 1.5	19.6 ± 0.6	36.0 ± 0.3	124.4 ± 11.6	6 ± 4	11.0 ± 0.2	20.2 ± 3.9	
	1,000	6	743** ± 23	73 ± 11	15.0* ± 0.5	42.0 ± 1.5	56.7 ± 2.6	20.2 ± 0.8	35.8 ± 0.5	135.7* ± 6.1	12 ± 8	10.9 ± 0.3	20.2 ± 1.7	

Mean ± S.D.

\* : Significantly different from Vehicle control at P<0.05.

\*\* : Significantly different from Vehicle control at P<0.01.

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Table 4 -Continued  
Hematology

Sex	Exp. group (mg/kg/day)	Number of animals	Differentiation of leukocyte (%)				
			N-Band	N-Seg	Rosine	Baso	Lymph
Male	Vehicle control	6	0.1 ±0.2	4.4 ±2.4	0.3 ±0.4	0.0 ±0.0	94.8 ±2.9
	8	6	0.2 ±0.3	6.1 ±2.7	0.4 ±0.4	0.0 ±0.0	93.2 ±3.2
	40	6	0.0 ±0.0	6.0 ±1.0	0.7 ±0.6	0.0 ±0.0	93.3 ±1.4
	200	6	0.0 ±0.0	5.0 ±3.0	0.3 ±0.4	0.0 ±0.0	94.4 ±2.9
	1,000	6	0.4* ±0.2	7.4 ±5.0	0.4 ±0.4	0.0 ±0.0	90.9 ±5.8
	Recovery	6	0.1 ±0.2	4.7 ±1.7	0.3 ±0.4	0.0 ±0.0	94.8 ±2.0
Female	Vehicle control	6	0.0 ±0.0	6.4 ±1.5	0.4 ±0.6	0.0 ±0.0	92.8 ±1.0
	200	6	0.1 ±0.2	7.0 ±3.1	0.5 ±0.4	0.0 ±0.0	92.1 ±3.0
	1,000	6	0.2 ±0.2	6.5 ±1.6	0.5 ±0.3	0.0 ±0.0	92.6 ±1.7
	Vehicle control	6	0.2 ±0.3	6.2 ±3.5	0.6 ±0.4	0.0 ±0.0	93.0 ±3.6
	8	6	0.1 ±0.2	5.5 ±1.7	0.6 ±0.9	0.0 ±0.0	93.5 ±1.6
	40	6	0.1 ±0.2	7.4 ±3.7	0.5 ±0.6	0.0 ±0.0	91.9 ±3.0
Female	200	6	0.1 ±0.2	7.0 ±2.5	0.3 ±0.4	0.0 ±0.0	92.3 ±2.6
	1,000	6	0.1 ±0.2	7.0 ±2.5	0.3 ±0.4	0.0 ±0.0	92.4 ±4.3
	Recovery	6	0.3 ±0.3	5.2 ±1.3	1.0 ±1.0	0.0 ±0.0	93.3 ±2.2
Male	Vehicle control	6	0.1 ±0.2	8.5 ±4.4	0.4 ±0.4	0.0 ±0.0	90.9 ±4.5
	200	6	0.4 ±0.4	6.2 ±3.7	0.8 ±0.8	0.0 ±0.0	92.4 ±4.3
	1,000	6	0.4 ±0.4	6.2 ±3.7	0.8 ±0.8	0.0 ±0.0	90.3 ±0.3
	Recovery	6	0.3 ±0.3	5.2 ±1.3	1.0 ±1.0	0.0 ±0.0	93.3 ±2.2

Mean ± S.D.  
\* : Significantly different from Vehicle control at P<0.05.  
\*\* : Significantly different from Vehicle control at P<0.01.

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Table 5 28-day repeated-dose oral toxicity study in rats  
Blood chemistry

Sex	Exp. group (mg/kg/day)	Number of animals	GOT (IU/l)	GPT (IU/l)	ALP (IU/l)	ChE (IU/l)	$\gamma$ -GTP (IU/l)	T-Chol (mg/dl)	TG (mg/dl)	Glucose (mg/dl)	$\gamma$ -protein (g/dl)	Albumin (g/dl)	A/G ratio
			Vehicle control	Vehicle control	Vehicle control	Vehicle control	Vehicle control	Vehicle control	Vehicle control	Vehicle control	Vehicle control	Vehicle control	Vehicle control
Male	Vehicle control	6	81 ±10	29 ±3	512 ±67	55 ±15	0.6 ±0.2	46 ±6	51 ±15	133.1 ±13.4	5.7 ±0.2	2.9 ±0.1	1.01 ±0.08
	8	6	87 ±9	31 ±2	466 ±77	52 ±17	0.5 ±0.3	42 ±4	46 ±10	125.3 ±13.0	5.8 ±0.2	2.9 ±0.1	1.01 ±0.06
	40	6	87 ±13	31 ±2	529 ±58	41 ±6	0.5 ±0.2	47 ±7	48 ±13	116.2 ±17.1	5.6 ±0.3	2.9 ±0.1	1.07 ±0.05
	200	6	82 ±9	30 ±4	490 ±57	51 ±8	0.7 ±0.1	46 ±6	66 ±20	111.8* ±13.8	5.7 ±0.1	2.9 ±0.1	1.02 ±0.03
	1,000	6	80 ±4	32 ±2	476 ±67	48 ±10	0.6 ±0.1	50 ±9	58 ±11	108.3* ±12.6	5.7 ±0.2	3.0 ±0.1	1.08 ±0.04
Recovery	Vehicle control	6	77 ±7	29 ±3	373 ±43	44 ±13	0.6 ±0.4	44 ±5	63 ±11	150.8 ±15.6	5.8 ±0.2	2.9 ±0.1	1.02 ±0.06
	200	6	81 ±20	28 ±4	336 ±36	48 ±11	0.6 ±0.2	47 ±7	61 ±13	132.6 ±16.2	6.0 ±0.1	2.9 ±0.1	0.93 ±0.06
	1,000	6	77 ±8	28 ±3	342 ±40	44 ±12	0.6 ±0.3	45 ±10	46 ±16	129.7 ±17.6	5.9 ±0.2	2.9 ±0.1	0.97 ±0.06
Vehicle control	6	88 ±10	26 ±4	310 ±34	238 ±88	0.9 ±0.1	52 ±14	29 ±4	116.5 ±11.1	5.8 ±0.2	3.1 ±0.2	1.14 ±0.05	
	8	6	83 ±10	25 ±3	278 ±69	269 ±64	0.8 ±0.2	58 ±7	27 ±6	122.6 ±8.2	6.0 ±0.2	3.2 ±0.1	1.13 ±0.05
	40	6	83 ±19	24 ±2	269 ±30	302 ±73	0.9 ±0.2	65 ±15	32 ±9	125.1 ±18.0	6.1 ±0.1	3.2 ±0.1	1.13 ±0.08
	200	6	87 ±21	24 ±2	265 ±45	315 ±97	0.8 ±0.2	58 ±12	31 ±7	121.7 ±14.0	6.1 ±0.4	3.3 ±0.2	1.17 ±0.05
	1,000	6	83 ±12	26 ±1	249 ±31	194 ±41	0.9 ±0.3	57 ±8	41* ±10	103.8 ±22.5	5.9 ±0.3	3.1 ±0.2	1.13 ±0.04
Recovery	Vehicle control	6	92 ±13	25 ±4	200 ±28	351 ±110	0.8 ±0.1	55 ±9	35 ±11	124.4 ±12.8	6.3 ±0.2	3.3 ±0.2	1.12 ±0.07
	200	6	80 ±17	26 ±4	196 ±42	404 ±142	0.6 ±0.3	59 ±9	33 ±16	135.9 ±16.5	6.4 ±0.3	3.3 ±0.2	1.05 ±0.06
	1,000	6	87 ±13	24 ±2	171 ±27	238 ±80	0.7 ±0.1	60 ±8	31 ±6	127.6 ±10.4	6.2 ±0.3	3.2 ±0.2	1.06 ±0.07

Mean ± S.D.

\* : Significantly different from Vehicle control at P<0.05.

\*\* : Significantly different from Vehicle control at P<0.01.

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Table 5 -Continued  
Blood chemistry

Sex	Exp.-group (mg/kg/day)	Number of animals	BUN (mg/dl)	Creatinine (mg/dl)	T-Bil. (mg/dl)	Ca (mg/dl)	IP (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
	Vehicle control	6	14.1 ± 1.7	0.45 10.07	0.18 10.03	9.6 10.3	8.2 10.5	144 11	4.6 1.1	106.2 10.1
Male	8	6	14.7 ± 2.2	0.43 10.05	0.20 10.02	9.5 10.2	8.0 10.2	145 11	4.8 1.1	106.1 10.2
	40	6	13.8 ± 1.2	0.41 10.05	0.20 10.02	9.4 10.2	7.7 10.5	145 11	4.6 1.1	107.3 10.3
	200	6	14.6 ± 1.0	0.39 10.03	0.22 10.04	9.6 10.1	7.7 10.7	144 11	4.6 1.1	106.4 10.3
	1,000	6	14.4 ± 1.7	0.40 10.05	0.25** 10.04	9.8 10.2	8.4 10.3	144 11	4.5 1.1	106.0 10.2
	Recovery Vehicle control	6	16.4 ± 3.7	0.54 10.03	0.15 10.02	9.5 10.3	7.8 10.5	143 11	4.3 1.1	106.7 10.2
	200	6	13.7 ± 1.8	0.47** 10.02	0.18* 10.01	9.6 10.2	7.2 10.5	144 11	4.6 1.1	107.2 10.3
	1,000	6	15.2 ± 1.6	0.47** 10.04	0.19* 10.02	9.6 10.2	7.5 10.2	143 11	4.4 1.1	106.8 10.3
	Vehicle control	6	14.3 ± 1.8	0.46 10.03	0.18 10.01	9.7 10.2	7.9 10.5	143 11	4.4 1.1	109.3 10.4
	8	6	13.8 ± 1.3	0.47 10.06	0.18 10.02	9.8 10.3	7.9 10.6	142 11	4.5 1.1	108.5 10.3
	40	6	15.7 ± 1.9	0.50 10.04	0.18 10.01	9.9 10.3	7.7 10.6	143 12	4.3 1.2	107.9 10.2
	200	6	13.1 ± 1.3	0.43 10.04	0.20 10.02	9.9 10.2	7.5 10.3	142 11	4.4 1.1	106.7** 10.5
	1,000	6	13.7 ± 1.7	0.39* 10.04	0.21 10.02	9.8 10.3	7.9 10.2	143 12	4.4 1.2	106.8** 10.2
	Recovery Vehicle control	6	15.4 ± 2.1	0.50 10.04	0.17 10.03	9.7 10.4	6.5 10.5	142 11	4.5 1.1	108.7 10.3
	200	6	15.6 ± 1.8	0.49 10.05	0.19 10.04	10.0 10.5	6.7 10.8	142 11	4.6 1.1	108.4 10.4
	1,000	6	14.8 ± 0.8	0.49 10.04	0.17 10.02	9.8 10.3	6.6 10.7	141 11	4.7 1.1	108.9 10.3

Mean ± S.D.

\* : Significantly different from Vehicle control at P<0.05.

\*\* : Significantly different from Vehicle control at P<0.01.

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Table 6 28-day repeated-dose oral toxicity study - rats  
Urinalysis

Sex	Exp. group (mg/kg/day)	Number of animals	Volume <sup>a)</sup> (ml)	Color			pH	Protein	Ketones	Bilirubin	Occult Blood	Glucose	Urobilinogen (EU/dl)	-	-
				SY	Y	YB									
Vehicle control	6	19	4 2 0 0 0 0	3 3 0 0 0 0	0 3 3 0 0 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0
8	6	±11	1 5 0 0 0 0	3 3 0 0 0 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0	0 0 4 1 1 0
40	6	18	5 1 0 0 0 0	4 2 0 0 0 0	0 4 2 0 0 0	0 4 2 0 0 0	0 4 2 0 0 0	0 4 2 0 0 0	0 4 2 0 0 0	0 4 2 0 0 0	0 4 2 0 0 0	0 4 2 0 0 0	0 4 2 0 0 0	0 4 2 0 0 0	0 4 2 0 0 0
200	6	16	4 2 0 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0
1,000	6	15	5 1 0 0 1 0	2 3 0 5 0 0	0 1 0 0 0 0	0 1 0 0 0 0	0 1 0 0 0 0	0 1 0 0 0 0	0 1 0 0 0 0	0 1 0 0 0 0	0 1 0 0 0 0	0 1 0 0 0 0	0 1 0 0 0 0	0 1 0 0 0 0	0 1 0 0 0 0
Male		±6	±9												
Recovery															
Vehicle control	6	10	2 3 0 1 0 0	3 3 0 2 0 0	0 2 0 4 0 0	0 2 0 4 0 0	0 2 0 4 0 0	0 2 0 4 0 0	0 2 0 4 0 0	0 2 0 4 0 0	0 2 0 4 0 0	0 2 0 4 0 0	0 2 0 4 0 0	0 2 0 4 0 0	0 2 0 4 0 0
200	6	14	4 2 0 0 0 0	3 3 0 4 1 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0
1,000	6	13	3 3 0 0 0 0	1 5 0 0 0 0	0 1 4 0 1 0	0 1 4 0 1 0	0 1 4 0 1 0	0 1 4 0 1 0	0 1 4 0 1 0	0 1 4 0 1 0	0 1 4 0 1 0	0 1 4 0 1 0	0 1 4 0 1 0	0 1 4 0 1 0	0 1 4 0 1 0
Female		±9	±6												
Vehicle control	6	15	5 1 0 0 0 0	0 5 1 0 0 0	0 6 0 0 0 0	0 6 0 0 0 0	0 6 0 0 0 0	0 6 0 0 0 0	0 6 0 0 0 0	0 6 0 0 0 0	0 6 0 0 0 0	0 6 0 0 0 0	0 6 0 0 0 0	0 6 0 0 0 0	0 6 0 0 0 0
8	6	15	5 1 0 0 0 0	0 4 2 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0
40	6	11	4 2 0 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0
200	6	11	2 4 0 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0	0 5 1 0 0 0
1,000	6	12	3 2 1 0 0 0	0 4 2 0 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0
Recovery															
Vehicle control	6	10	3 3 0 0 0 0	0 5 1 0 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0	0 4 1 1 0 0
200	6	11	3 3 0 0 0 0	0 6 0 1 2 0	0 6 0 1 2 0	0 6 0 1 2 0	0 6 0 1 2 0	0 6 0 1 2 0	0 6 0 1 2 0	0 6 0 1 2 0	0 6 0 1 2 0	0 6 0 1 2 0	0 6 0 1 2 0	0 6 0 1 2 0	0 6 0 1 2 0
1,000	6	11	3 3 0 0 0 0	1 3 2 0 4 0	1 3 2 0 4 0	1 3 2 0 4 0	1 3 2 0 4 0	1 3 2 0 4 0	1 3 2 0 4 0	1 3 2 0 4 0	1 3 2 0 4 0	1 3 2 0 4 0	1 3 2 0 4 0	1 3 2 0 4 0	1 3 2 0 4 0

a) Mean±S.D.  
\* : Significantly different from Vehicle control at P<0.05.  
\*\* : Significantly different from Vehicle control at P<0.01.  
SY : Slightly yellow  
Y : Yellow  
YB : Yellow brown  
B : Brown

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Table 7 28-day repeated-dose oral toxicity study in rats  
Absolute organ weights

Sex	Exp. Group (mg/kg/day)	Number of animals	Spleen (g)	Liver (g)	Kidney (g)	Brain (g)	Testis (g)	Adrenal gland (mg)	Ovary (mg)	Body weight (g)
Vehicle control	6	0.55	9.79	2.44	1.90	2.83	50.6	-	-	320.0
8	6	0.57	9.53	2.51	1.92	2.84	54.0	-	-	320.7
40	6	0.52	8.97	2.34	1.90	2.91	45.9	-	-	298.6
200	6	0.68	10.17	2.55	1.89	2.79	49.3	-	-	323.0
1,000	6	0.67	10.08	2.36	0.07	0.26	5.7	-	-	323.0
Recovery Vehicle control	6	0.64	10.17	2.47	1.92	3.22	53.9	-	-	375.0
200	6	0.67	9.98	2.62	1.97	3.06	50.1	-	-	364.3
1,000	6	0.73	10.71	2.64	1.97	0.23	4.8	-	-	358.7
Vehicle control	6	0.41	6.37	1.66	1.77	-	57.6	83.3	12.4	202.9
8	6	0.42	6.97	1.56	1.78	-	57.7	80.0	19.3	24.0
40	6	0.42	6.02	1.59	1.73	-	77.4	10.8	9.2	190.5
200	6	0.46	6.79	1.74	1.79	-	54.2	9.1	16.2	195.5
1,000	6	0.43	8.34**	1.71	1.82	-	59.1	79.4	12.3	196.6
Recovery Vehicle control	6	0.45	6.27	1.66	1.85	-	61.7	93.4	8.7	226.3
200	6	0.44	6.96	1.88	1.81	-	67.6	94.1	8.0	228.0
1,000	6	0.51	7.22	1.77	1.84	-	85.3	99.8	13.1	233.9

Mean  $\pm$  S.D.

\* : Significantly different from Vehicle control at P<0.05.

\*\* : Significantly different from Vehicle control at P<0.01.

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Table 8 28-day repeated-dose oral toxicity study in rats  
Relative organ weights

Sex	Exp. group (mg/kg/day)	Number of animals	Relative organ weights			Adrenal gland (mg/100g)				Ovary (mg/100g)	Body weight (g)
			Spleen (g/100g)	Liver (g/100g)	Kidney (g/100g)	Brain (g/100g)	Testis (g/100g)	Adrenal gland (mg/100g)	Ovary (mg/100g)		
Male	Vehicle control	6	0.17 ±0.03	3.05 ±0.22	0.76 ±0.06	0.60 ±0.05	0.89 ±0.07	15.9 ±1.7	-	320.0	-
	8	6	0.18 ±0.03	2.97 ±0.15	0.78 ±0.05	0.60 ±0.03	0.92 ±0.05	16.8 ±1.3	-	320.7	-
	40	6	0.17 ±0.02	3.00 ±0.17	0.78 ±0.04	0.64 ±0.03	0.98 ±0.08	15.4 ±2.1	-	298.6	-
	200	6	0.20 ±0.01	3.15 ±0.14	0.79 ±0.04	0.59 ±0.03	0.86 ±0.08	15.3 ±1.7	-	323.0	-
	1,000	6	0.19 ±0.02	3.81** ±0.07	0.82 ±0.05	0.63 ±0.04	0.87 ±0.05	14.6 ±1.5	-	296.7	-
	Recovery Vehicle control	6	0.17 ±0.02	2.71 ±0.05	0.66 ±0.07	0.51 ±0.03	0.86 ±0.06	14.4 ±2.8	-	375.0	-
	200	6	0.19 ±0.02	2.74 ±0.09	0.72 ±0.05	0.54 ±0.02	0.84 ±0.07	13.8 ±1.3	-	364.3	-
	1,000	6	0.20 ±0.03	2.98** ±0.09	0.74* ±0.03	0.55 ±0.04	0.78 ±0.04	14.7 ±2.1	-	19.0	-
	Vehicle control	6	0.20 ±0.02	3.14 ±0.18	0.82 ±0.04	0.87 ±0.04	-	28.4 ±3.1	41.0 ±5.6	-	24.0
	8	6	0.22 ±0.03	3.08 ±0.17	0.81 ±0.05	0.92 ±0.04	-	29.8 ±3.0	41.4 ±6.1	-	193.5
Female	40	6	0.22 ±0.03	3.16 ±0.20	0.83 ±0.08	0.91 ±0.05	-	28.5 ±4.9	40.6 ±3.0	-	190.5
	200	6	0.23 ±0.04	3.47* ±0.17	0.88 ±0.06	0.92 ±0.03	-	30.2 ±3.4	40.6 ±5.9	-	16.2
	1,000	6	0.22 ±0.03	4.25** ±0.13	0.87 ±0.07	0.93 ±0.08	-	30.3 ±3.2	44.2 ±6.4	-	195.5
	Recovery Vehicle control	6	0.20 ±0.03	2.77 ±0.12	0.74 ±0.05	0.82 ±0.03	-	27.4 ±1.6	41.4 ±3.4	-	226.3
	200	6	0.19 ±0.02	3.05 ±0.28	0.82* ±0.06	0.80 ±0.04	-	28.7 ±3.8	41.4 ±3.9	-	17.8
1,000	1,000	6	0.22 ±0.02	3.08* ±0.16	0.76 ±0.04	0.79 ±0.03	-	27.8 ±2.7	42.8 ±6.6	-	228.0
										-	13.1

Mean ± S.D.

\* : Significantly different from Vehicle control at P<0.05.

\*\* : Significantly different from Vehicle control at P<0.01..

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 Table 9 28-day repeated-dose oral toxicity study in rats  
 Gross pathological findings

Findings	Male												Female														
	Vehicle			Vehicle			control			control			Vehicle			control			(Recovery)			(Recovery)			(kg/kg/day)		
	control	(Recovery)	ta*	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta													
6**	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		
Kidney																											
Apparent spotty pattern of surface	0	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Pelvic dilatation	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Rough surface	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0		
Glandular stomach																											
Blackish spot of mucosa	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Roughening of mucosa	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Skin																											
Scab formation	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		

\* ta. terminal autopsy.  
 \*\* Number of animals examined.

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Table 10 28-day repeated-dose oral toxicity study in  
Histopathological findings

Findings	Grade	Male						Female					
		Vehicle		Vehicle		Vehicle		Vehicle		Vehicle		(Recovery)	
		control	(Recovery)	8	40	200	1,000	control	control	8	40	200	1,000
		ta*	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	(Recovery) (mg/kg/day)
Liver		2/6***	1/6	-	-	2/6	2/6	2/6	0/6	1/6	-	2/6	1/6
No abnormalities detected													0/6
Granulation tissue with calcification	+	0/6	0/6	-	-	0/6	0/6	1/6	0/6	0/6	-	0/6	0/6
Microgranuloma	t	3/6	3/6	-	-	4/6	3/6	0/6	3/6	3/6	-	3/6	4/6
	+	0/6	2/6	-	-	0/6	1/6	0/6	1/6	2/6	-	1/6	1/6
Perilobular lipid droplets	t	1/6	0/6	-	-	0/6	1/6	0/6	0/6	2/6	-	0/6	1/6
	+	1/6	0/6	-	-	0/6	0/6	0/6	0/6	4/6	1/6	1/6	2/6
Swelling of hepatocytes	+	0/6	0/6	-	-	0/6	0/6	3/6	0/6	0/6	-	0/6	0/6
Spleen		6/6	-	-	-	-	-	6/6	-	6/6	-	-	-
No abnormalities detected													6/6
Kidney													
No abnormalities detected		6/6	5/6	5/6	5/6	2/6	5/6	0/6	5/6	5/6	-	-	-
Cyst formation		0/6	1/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	-	-	-
Fibrosis	+	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	1/6	-	-	-
Increased eosinophilic bodies	+	0/6	0/6	0/6	0/6	0/6	0/6	1/6	1/6	0/6	-	-	-
	++	0/6	0/6	0/6	0/6	0/6	0/6	3/6	0/6	0/6	-	-	-
Pelvic dilatation		0/6	0/6	1/6	1/6	1/6	1/6	0/6	0/6	0/6	-	-	-
Pyelonephritis	++	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	-	-	-
Heart													
No abnormalities detected		6/6	-	-	-	-	-	6/6	-	6/6	-	-	-

\* ta, terminal autopsy.

\*\* Number of animals autopsied.

\*\*\* Number of animals affected / Number of animals examined.

t, very slight; +, slight; ++, moderate; +++, severe.

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Table 10 - Continued  
Histopathological findings

Findings	Male						Female					
	Vehicle control		8 (Recovery)		200 (Recovery)		Vehicle control		8 (Recovery)		200 (Recovery)	
	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta
Grade	6	6	6	6	6	6	6	6	6	6	6	6
Forestomach												
No abnormalities detected	6/6	6/6	—	—	6/6	—	1/6	6/6	6/6	—	—	—
Mucosal degeneration	†	0/6	0/6	—	—	0/6	—	4/6	0/6	0/6	—	0/6
	†	0/6	0/6	—	—	0/6	—	1/6	0/6	0/6	—	0/6
Glandular stomach												
No abnormalities detected	6/6	6/6	—	—	6/6	0/1	6/6	6/6	6/6	—	—	—
Necrosis of mucosa	†	0/6	0/6	—	—	0/6	1/1	0/6	0/6	0/6	—	0/6
Duodenum												
No abnormalities detected	6/6	—	—	—	—	—	6/6	—	6/6	—	—	—
Jejunum												
No abnormalities detected	6/6	—	—	—	—	—	6/6	—	6/6	—	—	—
Ileum												
No abnormalities detected	6/6	—	—	—	—	—	6/6	—	6/6	—	—	—
Cecum												
No abnormalities detected	6/6	—	—	—	—	—	6/6	—	6/6	—	—	—
Colon												
No abnormalities detected	6/6	—	—	—	—	—	6/6	—	6/6	—	—	—
Rectum												
No abnormalities detected	6/6	—	—	—	—	—	6/6	—	6/6	—	—	—
Testis												
No abnormalities detected	6/6	6/6	—	—	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6

000297

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Table 10 — Continued  
Histopathological findings

Findings	Male						Female					
	Vehicle control	Vehicle (Recovery)	Male			Vehicle control	Vehicle (Recovery)	Female			(Recovery) (mg/kg/day)	(Recovery) (mg/kg/day)
			8	40	200			ta	ta	ta		
Grade	6	6	6	6	6	6	6	6	6	6	6	6
Adrenal												
No abnormalities detected	6/6	—	—	—	—	6/6	—	6/6	—	—	—	6/6
Skin												
No abnormalities detected	—	—	—	—	—	—	0/1	—	—	—	—	—
Scab formation	+	—	—	—	—	—	1/1	—	—	—	—	—

0298

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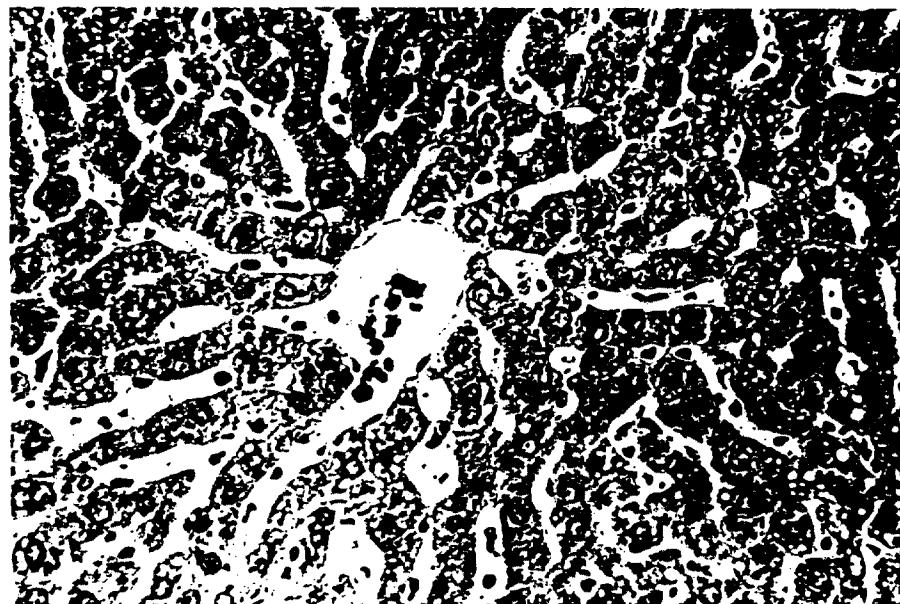


Photo. 1 Liver of a male rat given vehicle orally for 28 days.  
Normal.  
No. 2 animal. HE.  $\times 360$ .

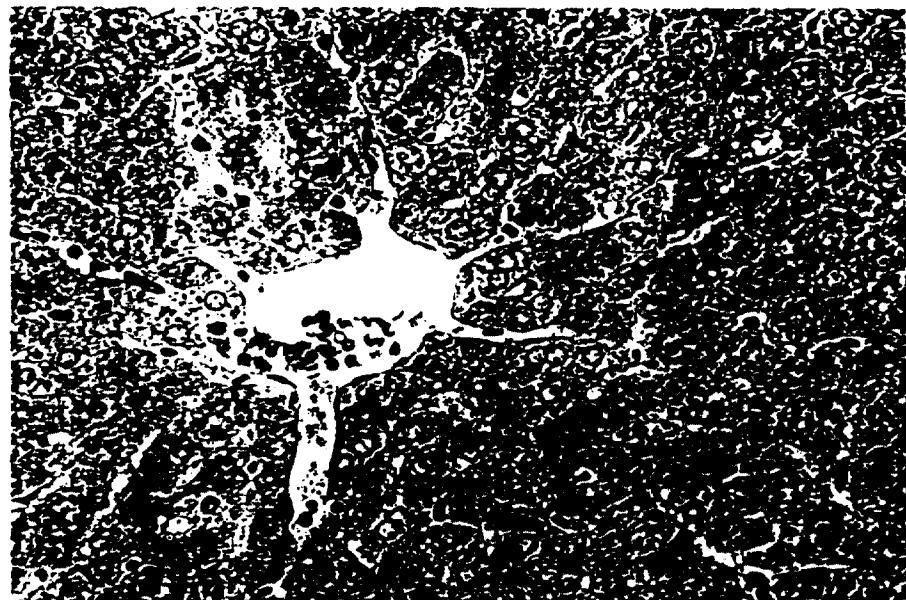


Photo. 2 Liver of a male rat given test substance at dose level  
of 1,000mg/kg/day orally for 28 days.  
Swelling of hepatocytes.  
No. 37 animal. HE.  $\times 360$ .  
*218*

000299

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Photo. 3    Kidney of a male rat given vehicle orally for 28 days.  
Normal.  
No. 1 animal. HE.     $\times 360$ .

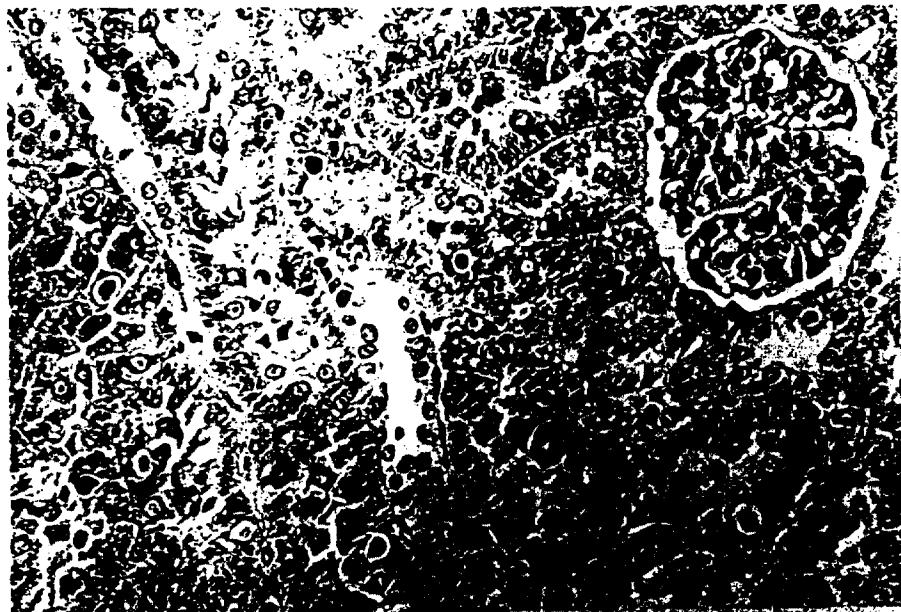


Photo. 4    Kidney of a male rat given test substance at dose level  
of 1,000mg/kg/day orally for 28 days.  
Increased eosinophilic bodies.  
No. 40 animal. HE.     $\times 360$ .

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GUS300

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Photo. 5 Forestomach of a male rat given vehicle orally for  
28 days.

Normal.

No. 1 animal. HE. X180

CC0301

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Addendum 1    28-day repeated-dose oral toxicity study in rats  
 Clinical signs  
 Vehicle control

Signs	Sex	Administration				Recovery	
		1	2	3	4 (weeks)	1	2 (weeks)
No abnormalities detected	Male	1-12*	1-12	1-12	1-12	7-12	7-12
	Female	49-60	49-60	49-60	49-60	55-60	55-60

\* Animal number.

0302

[ B11-0301 ]

Addendum 1 - Continued  
8mg/kg/day

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Signs	Sex	Administration				Recovery	
		1	2	3	4 (weeks)	1	2
No abnormalities detected							
Male		13-18*	13-18	13-18	13-16,18		
Female		61-66	61-66	61-66	61-66		
Loss of hair (neck)	Male					17	
	Female						
Scab formation (neck)	Male					17	
	Female						

\* Animal number.

0303

Addendum 1 — Continued  
40mg/kg/day

B11-0301

Signs	Sex	Administration				Recovery	
		1	2	3	4 (weeks)	1	2 (weeks)
No abnormalities detected	Male	19-24*	19-24	19-24	19-24	67-72	67-72
	Female	67-72	67-72	67-72	67-72		

\* Animal number.

0304

Addendum 1 - Continued  
200mg/kg/day

B11-0301

Signs	Sex	Administration				Recovery	
		1	2	3	4 (weeks)	1	2 (weeks)
No abnormalities detected						31-36 79-84	31-36 79-84
	Male	25, 26, 32*					
	Female						
Salivation	Male	27-31, 33-36	25-36	25-36	25-36		
	Female	73-84	73-84	73-84	73-84		
Decreased spontaneous locomotion	Male		25-27, 30	29, 30, 33-36	25, 28, 30, 34, 35		
	Female						
Decreased respiratory rate	Male			35	34		
	Female						

\* Animal number.

0305

4 -

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Addendum 1 — Continued  
1,000mg/kg/day

B11-0301

Signs	Sex	Administration				Recovery	
		1	2	3	4 (weeks)	1	2 (weeks)
No abnormalities detected						45*	43-46, 48
	Male					92-96	91-96
	Female						
Salivation	Male	37-48	37-48	37-48	37-48	37-48	37-48
	Female	85-96	85-96	85-96	85-96	85-96	85-96
Decreased spontaneous locomotion	Male	37-48	37-39-48	37-48	37-39-46, 48	37-39-46, 48	37-39-46, 48
	Female	85-96	85-87, 89-96	85-87, 89-96	85-87, 89-94-96	85-86, 88-89, 91-92, 94-96	85-86, 88-89, 91-92, 94-96
Decreased respiratory rate	Male	37, 40-47	37, 40-42, 44, 46	37, 39, 41, 43-46	37, 39-41, 44, 46	39-41, 44, 46	39-41, 44, 46
	Female	85-87, 89, 91, 92, 94, 96	91, 95, 96	92, 95	92, 95	85, 89, 91, 94, 96	85, 89, 91, 94, 96
Soiled around nose and mouth	Male		37, 38, 45, 46	37, 46-48	41, 45, 47		
	Female		91, 92	87, 89, 91, 94, 96			
Soft stool	Male	40, 41			38, 40, 47		
	Female						
Hunchback	Male			39, 45		37, 44, 45	
	Female			85, 86, 89, 92, 94, 95		85, 86, 89	
Mark of reddish tear	Male			45		46	
	Female						
Reddish tear	Male			46			
	Female						
Ptosis	Male			44			
	Female						
Soiled around anus	Male				47		47
	Female				91		91

\* Animal number.

0306

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Addendum 1 - Continued  
1,000mg/kg/day

B11-0301

Signs	Sex	Administration				Recovery	
		1	2	3	4 (weeks)	1	2 (weeks)
Loss of hair	Male			37,43*		37,43	
(mandible)	Female			85,91,92		85,91,92	
Loss of hair	Male			44,48		39,43,44,48	
(neck)	Female					43,44,48	
Scab formation	Male			43,44,48		39,43,44,46,48	
	Female					43,44,46,48	
	(neck)						

\* Animal number.

0307















Addendum 3 -Continued  
Food consumption(g/rat/day)

Sex	Exp. Group (mg/kg/day)	Animal No.	Recovery			14 (days)
			4	8	11	
Male	Vehicle control	7	26.9	26.3	24.2	25.6
		8	24.7	27.8	25.8	27.2
		9	25.8	27.1	28.5	28.7
	200	10	24.4	23.9	23.7	25.1
		11	24.3	25.9	25.1	26.3
		12	31.3	30.4	28.5	30.0
		31	28.2	27.6	26.5	26.0
		32	22.0	22.7	21.2	23.4
	1,000	33	23.8	23.8	23.4	26.6
		34	26.6	26.0	24.4	25.7
Female	Vehicle control	35	24.3	24.7	24.2	25.2
		36	29.7	27.9	29.0	28.2
		43	28.8	28.4	28.6	28.5
		44	29.8	29.8	28.6	28.8
	200	45	27.1	26.9	25.1	25.2
		46	31.0	29.3	28.2	29.2
		47	26.2	26.0	25.0	25.8
		48	30.0	27.9	26.7	26.4
		55	18.6	19.8	18.1	20.3
	1,000	56	18.9	19.7	18.6	18.4
Female	Vehicle control	57	16.2	16.9	16.4	17.1
		58	19.6	19.5	18.3	18.8
		59	19.0	18.5	18.4	17.8
		60	20.8	22.2	19.5	22.0
		79	16.9	17.8	17.7	19.0
	200	80	18.2	19.5	17.8	18.5
		81	21.2	20.8	21.6	20.1
		82	18.4	18.1	16.5	20.4
		83	18.1	19.5	21.1	20.0
		84	25.5	23.7	22.8	23.1
1,000	Vehicle control	91	21.1	22.1	22.6	21.4
		92	21.5	21.0	21.0	22.4
		93	21.0	20.9	22.3	22.2
		94	21.1	22.6	21.7	22.5
		95	18.5	19.1	20.3	18.4
1,000		96	22.4	23.1	24.5	21.7

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B11-0301



Addendum 4 -Continued  
Hematology

[B11-0301]

Sex	Exp. group (mg/kg/day)	Animal No.		WBC ( $\times 10^3/\text{mm}^3$ )	Hb (g/dl)	Ht (%)	MCV ( $\mu\text{m}^3$ )	MCH (pg)	MCHC (%)	Platelet ( $\times 10^4/\text{mm}^3$ )	Reticulo (%)	PT (sec)	APTT (sec)
		RBC ( $\times 10^6/\text{mm}^3$ )	( $\times 10^4/\text{mm}^3$ )										
37	714	94	14.3	40.6	56.9	20.0	35.2	140.7	24	18.6	30.9		
38	659	141	14.1	40.5	61.5	21.4	34.8	123.3	14	16.5	31.5		
39	708	116	14.1	40.1	56.6	19.9	35.2	122.6	18	17.1	31.1		
40	704	102	13.5	40.8	58.0	19.2	33.1	133.5	30	17.9	31.0		
41	736	98	14.6	42.3	57.5	19.8	34.5	167.0	24	17.5	39.3		
42	774	89	14.2	42.6	55.0	18.3	33.3	131.0	20	19.0	32.6		
<b>Male</b>		<b>Recovery</b>											
43	765	130	15.4	46.0	60.1	20.1	33.5	102.6	10	14.0	23.2		
44	763	111	15.1	42.2	55.3	19.8	35.8	114.2	11	13.8	27.6		
45	738	123	15.1	43.5	58.9	20.5	34.7	104.1	14	15.0	28.0		
46	797	102	15.1	43.3	54.3	18.9	34.9	100.8	8	17.9	25.3		
47	857	84	15.9	45.5	53.1	18.6	34.9	130.8	4	19.7	26.6		
48	768	119	15.1	44.2	57.6	19.7	34.2	111.1	19	13.8	27.9		

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Addendum 4 -Continued  
Hematology

BII-0301

Sex	Exp. group (kg/day)	Animal No.	RBC (x10 <sup>4</sup> /mm <sup>3</sup> )	WBC (x10 <sup>2</sup> /mm <sup>3</sup> )	Hb (g/dl)	Ht (%)	MCV (μm <sup>3</sup> )	MCH (pg)	MCHC (%)	Platelet (x10 <sup>4</sup> /mm <sup>3</sup> )	Reticulo (%)	P.T. (sec)	APTT (sec)
	85	704	94	14.2	39.6	56.3	20.2	35.9	124.5	17	11.8	26.7	
	86	679	75	13.5	37.9	55.8	19.9	35.6	125.2	21	12.6	32.8	
	87	683	69	14.0	38.1	55.8	20.5	36.7	110.1	24	12.5	24.5	
	88	679	50	13.0	36.9	54.3	19.1	35.2	126.3	20	12.4	24.8	
	89	748	101	14.3	40.7	54.4	19.1	35.1	117.2	16	10.9	24.1	
	90	749	102	14.4	40.2	53.7	19.2	35.8	117.6	19	10.4	22.7	
<hr/>													
Female													
	91	713	62	15.0	41.7	58.5	21.0	36.0	127.6	27	11.0	16.9	
	92	719	81	14.8	41.7	58.0	20.6	35.5	141.6	7	10.7	21.0	
	93	755	59	14.3	39.5	52.3	18.9	36.2	140.0	7	11.2	20.0	
	94	763	86	15.6	43.1	56.5	20.4	36.2	135.8	13	10.4	21.6	
	95	766	80	15.2	42.2	55.1	19.8	36.0	128.8	6	11.3	21.4	
	96	739	72	15.3	44.0	59.5	20.7	34.8	140.2	9	10.7	20.3	

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Addendum 4 -Continued  
Hematology

BII-0301

Sex	Exp. group (mg/kg/day)	Animal No.	W-Band	Differentiation of leukocyte (%)				
				N-Seg	Eosino	Baso	Lymph	Mono
Vehicle control	1	0.0	8.0	1.0	0.0	90.0	1.0	
	2	0.5	3.0	0.0	0.0	96.5	0.0	
	3	0.0	6.5	0.0	0.0	93.0	0.5	
	4	0.0	4.5	0.5	0.0	95.0	0.0	
	5	0.0	2.0	0.5	0.0	97.0	0.5	
	6	0.0	2.5	0.0	0.0	97.5	0.0	
	7	0.0	6.0	0.0	0.0	94.0	0.0	
	8	0.0	4.5	0.5	0.0	95.0	0.0	
	9	0.0	2.0	0.0	0.0	98.0	0.0	
	10	0.5	3.5	0.0	0.0	96.0	0.0	
Male	11	0.0	6.0	0.0	0.0	93.5	0.5	
	12	0.0	6.0	1.0	0.0	92.5	0.5	
	13	0.0	8.0	0.5	0.0	91.0	0.5	
	14	0.5	6.0	1.0	0.0	92.5	0.0	
	15	0.0	4.0	0.0	0.0	96.0	0.0	
	16	0.0	2.5	0.5	0.0	97.0	0.0	
	17	0.5	10.0	0.5	0.0	88.5	0.5	
	18	0.0	6.0	0.0	0.0	94.0	0.0	
	19	0.0	7.5	1.0	0.0	91.5	0.0	
	20	0.0	5.5	1.0	0.0	93.0	0.5	
200	21	0.0	4.5	0.0	0.0	95.5	0.0	
	22	0.0	6.0	0.5	0.0	93.5	0.0	
	23	0.0	6.0	0.0	0.0	94.0	0.0	
	24	0.0	6.5	1.5	0.0	92.0	0.0	
	25	0.0	5.5	1.0	0.0	93.0	0.5	
	26	0.0	4.5	0.0	0.0	95.5	0.0	
	27	0.0	2.0	0.5	0.0	97.5	0.0	
	28	0.0	7.5	0.0	0.0	92.5	0.0	
	29	0.0	1.5	0.5	0.0	97.5	0.5	
	30	0.0	9.0	0.0	0.0	90.5	0.5	
Recovery	31	0.0	6.0	0.0	0.0	93.0	1.0	
	32	0.0	4.0	1.5	0.0	94.0	0.5	
	33	0.0	8.5	0.0	0.0	91.5	0.0	
	34	0.0	6.0	0.0	0.0	94.0	0.0	
	35	0.0	7.5	0.5	0.0	92.0	0.0	
	36	0.0	6.5	0.5	0.0	92.5	0.5	

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Addendum 4 -Continued  
Hematology

B11-0301

Sex	Exp. group (mg/kg/day)	Animal No.	W-Band	Differentiation of leukocyte (%)				
				N-Seg	Rosino	Baso	Lymph	Mono
Male	37	0.5	6.5	0.0	0.0	92.5	0.5	
	38	0.5	13.0	0.5	0.0	83.0	3.0	
	39	0.5	12.5	0.5	0.0	86.5	0.0	
	40	0.5	9.0	1.0	0.0	89.0	1.0	
	41	0.5	2.0	0.0	0.0	97.5	0.0	
	42	0.5	1.5	0.5	0.0	97.0	0.5	
	Recovery							
	43	0.0	7.5	0.0	0.0	92.5	0.0	
	44	0.0	7.0	0.5	0.0	92.5	0.0	
	45	0.0	6.0	0.0	0.0	92.5	1.5	
	46	0.0	11.5	1.0	0.0	87.0	0.5	
	47	0.5	2.0	1.0	0.0	96.5	0.0	
	48	0.0	8.0	0.5	0.0	91.5	0.0	

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Addendum 4 -Continued  
Hematology

B11-0301

Sex	Exp. Group (ng/kg/day)	Animal No.	N-Band	Differentiation of leukocyte (%)				
				N-Seg	Rosino	Baso	Lymph	Mono
Vehicle control	4.9	4.9	0.0	6.0	0.5	0.0	93.0	0.5
	5.0	5.0	0.0	5.0	0.5	0.0	94.0	0.5
	5.1	5.1	0.5	8.5	0.0	0.0	91.0	0.0
	5.2	5.2	0.0	5.5	1.0	0.0	93.5	0.0
	5.3	5.3	0.0	5.5	0.5	0.0	94.0	0.0
	5.4	5.4	0.5	8.5	0.5	0.0	90.0	0.5
	5.5	Recovery	0.0	6.0	1.0	0.0	92.5	0.5
	5.6		0.5	4.0	0.0	0.0	95.5	0.0
	5.7		0.5	5.0	2.5	0.0	91.5	0.5
	5.8		0.0	7.0	0.5	0.0	91.5	1.0
Female	5.9		0.5	5.5	2.0	0.0	92.0	0.0
	6.0		0.0	3.5	0.0	0.0	96.5	0.0
	6.1		0.0	1.0	0.5	0.0	98.5	0.0
	6.2		0.0	6.0	1.0	0.0	92.5	0.5
	6.3		0.5	10.5	0.5	0.0	88.5	0.0
	6.4		0.5	6.0	0.0	0.0	93.5	0.0
	6.5		0.0	9.5	0.5	0.0	90.0	0.0
	6.6		0.0	4.0	1.0	0.0	95.0	0.0
	6.7		0.0	3.0	0.0	0.0	96.5	0.5
	6.8		0.0	5.0	1.5	0.0	93.0	0.5
200	6.9		0.5	5.5	0.0	0.0	93.5	0.5
	7.0		0.0	6.5	0.0	0.0	93.5	0.0
	7.1		0.0	5.0	2.0	0.0	93.0	0.0
	7.2		0.0	8.0	0.0	0.0	91.5	0.5
	7.3		0.0	4.0	1.0	0.0	95.0	0.0
	7.4		0.0	11.5	0.0	0.0	88.5	0.0
	7.5		0.0	10.0	0.0	0.0	90.0	0.0
	7.6		0.0	8.0	0.5	0.0	91.5	0.0
	7.7		0.0	9.0	0.0	0.0	90.5	0.5
	7.8	Recovery	0.5	2.0	1.5	0.0	96.0	0.0
200	7.9		0.0	9.5	0.0	0.0	90.5	0.0
	8.0		0.0	5.0	0.0	0.0	95.0	0.0
	8.1		0.0	5.5	0.5	0.0	94.0	0.0
	8.2		0.0	16.5	0.5	0.0	83.0	0.0
	8.3		0.0	5.5	0.5	0.0	94.0	0.0
	8.4		0.5	9.0	1.0	0.0	89.0	0.5

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Addendum 4 -Continued  
Hematology

Sex	Exp. group (kg/kg/day)	Animal No.	N-Band	Differentiation of Leukocyte (%)			
				N-Seg	Eosino	Baso	Lymph
Female	1,000	85	0.0	5.0	0.5	0.0	94.5
		86	0.5	6.0	0.0	0.0	93.0
		87	0.0	5.5	0.5	0.0	94.0
		88	0.0	10.0	1.0	0.0	89.0
		89	0.0	10.5	0.0	0.0	89.0
	Recovery	90	0.0	5.0	0.0	0.0	94.0
		91	0.5	12.5	1.5	0.0	85.0
		92	1.0	5.5	0.0	0.0	93.0
		93	0.5	5.5	0.0	0.0	94.0
		94	0.5	3.0	1.5	0.0	94.5
	95	95	0.0	2.5	0.0	0.0	97.5
		96	0.0	8.0	1.5	0.0	90.5

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Addendum 5 -Continued  
Blood chemistry

B11-0301

Sex	Exp. group (mg/kg/day)	Animal No.	GOT (IU/l)	GPT (IU/l)	ALP (IU/l)	ChE (IU/l)	$\gamma$ -GTP (IU/l)	T-Chol (ng/dl)	TG (ng/dl)	Glucose (mg/dl)	T-protein (g/dl)	Albumin (g/dl)	A/G ratio
Male	37	79	34	52.1	43	0.7	55	77	116.7	5.7	3.0	1.11	
	38	82	31	464	65	0.6	51	55	97.1	5.8	3.0	1.07	
	39	76	32	450	51	0.5	62	66	107.8	5.8	2.9	1.00	
	40	81	31	465	47	0.4	51	51	105.4	5.8	3.0	1.07	
	41	86	30	379	36	0.7	35	46	94.5	5.3	2.8	1.12	
	42	78	35	577	43	0.5	45	55	128.4	5.9	3.1	1.11	
	<u>Recovery</u>												
	43	73	24	375	46	0.3	49	31	136.3	5.6	2.7	0.93	
	44	79	33	386	41	0.2	42	52	126.4	5.8	2.9	1.00	
	45	80	28	371	64	0.5	37	33	103.9	5.8	2.8	0.93	
	46	80	30	318	39	0.7	63	76	121.3	6.1	2.9	0.91	
	47	65	27	292	29	1.1	40	43	156.8	6.1	3.1	1.03	
	48	74	28	312	44	0.8	41	42	133.6	5.7	2.9	1.04	

0325



Addendum 5 -Continued  
Blood chemistry

		B11-0301																					
Sex	Exp. group (mg/kg/day)	GOT (IU/l)		GPT (IU/l)		ALP (IU/l)		ChE (IU/l)		$\gamma$ -GTP (IU/l)		T-Chol (ng/dl)		TG (ng/dl)		Glucose (ng/dl)		T-protein (g/dl)		Albumin (g/dl)		A/G ratio	
		Animal No.	(IU/l)																				
	85	96	26	214	166	1.1	58	30	78.7	6.0	3.2	1.14											
	86	92	25	257	142	1.2	41	29	80.7	5.5	2.9	1.12											
	87	69	25	288	165	0.9	60	39	139.5	6.2	3.3	1.14											
	88	68	25	211	233	0.3	59	46	108.6	5.6	2.8	1.07											
	89	84	28	270	229	1.0	57	45	102.9	6.1	3.2	1.10											
	90	90	28	252	229	0.8	64	54	112.2	6.1	3.3	1.18											
1,000		Recovery																					
Female		91	108	24	209	156	0.7	56	32	126.5	6.1	3.1	1.03										
		92	84	21	152	129	0.8	60	34	140.2	5.9	3.0	1.07										
		93	96	25	152	324	0.5	56	34	117.3	6.2	3.2	1.13										
		94	86	26	140	309	0.7	76	38	130.9	6.6	3.5	1.14										
		95	69	24	195	236	0.6	55	24	114.0	6.0	3.2	1.14										
		96	80	24	178	271	0.9	54	23	136.5	6.5	3.2	0.97										

0327

Appendix 5 -Continued  
Blood chemistry

Sex	Exp. group ( $\text{mg/kg/day}$ )	Animal No.	BUN ( $\text{mg/dl}$ )	Creatinine ( $\text{mg/dl}$ )	T-Bil ( $\text{mg/dl}$ )	Ca ( $\text{mg/dl}$ )	IP ( $\text{mg/dl}$ )	Na ( $\text{mEq/l}$ )	K ( $\text{mEq/l}$ )	Cl ( $\text{mEq/l}$ )
Vehicle	1	13.7	0.49	0.19	9.0	8.2	144	4.5	108.6	
	2	16.7	0.51	0.15	9.0	9.0	144	4.5	105.1	
	3	15.5	0.50	0.18	9.6	8.3	144	4.8	105.1	
	4	12.1	0.40	0.24	9.7	7.4	145	4.6	105.9	
	5	12.9	0.34	0.15	9.7	8.1	145	4.8	107.6	
	6	13.7	0.48	0.17	9.7	8.3	144	4.6	104.9	
	Recovery									
	7	12.3	0.57	0.13	9.6	7.3	145	4.0	108.3	
	8	15.4	0.50	0.14	9.1	7.7	143	4.2	104.9	
	9	23.3	0.53	0.13	9.4	8.1	143	4.5	104.6	
Male	10	14.7	0.53	0.15	9.8	7.5	142	4.2	105.4	
	11	15.4	0.57	0.14	9.4	7.6	142	4.5	109.5	
	12	17.3	0.56	0.19	9.9	8.8	145	4.4	107.2	
	13	13.6	0.43	0.22	9.6	7.9	144	4.5	105.3	
	14	17.9	0.50	0.21	9.5	8.1	144	4.9	107.6	
	15	13.4	0.42	0.21	9.2	7.6	145	4.9	107.2	
	16	12.0	0.48	0.22	9.7	8.2	143	4.9	106.2	
	17	16.4	0.41	0.17	9.6	8.1	144	4.7	104.6	
	18	15.1	0.36	0.19	9.5	8.1	147	4.6	105.5	
	19	13.3	0.45	0.18	9.6	7.8	146	4.4	108.9	
200	20	13.9	0.41	0.19	9.6	6.9	146	4.2	108.6	
	21	15.2	0.36	0.21	9.2	8.1	145	4.7	106.3	
	22	12.6	0.37	0.21	9.4	7.3	144	4.9	107.4	
	23	14.5	0.47	0.17	9.2	8.0	145	4.5	106.6	
	24	12.0	0.37	0.21	9.6	8.0	145	4.7	106.0	
	25	13.4	0.36	0.28	9.8	7.4	144	4.6	106.7	
	26	14.4	0.36	0.22	9.7	7.6	144	4.4	107.4	
	27	14.9	0.37	0.24	9.5	7.1	144	4.4	106.4	
	28	14.8	0.42	0.22	9.5	7.3	145	4.2	108.0	
	29	16.0	0.42	0.22	9.6	9.0	143	5.0	104.9	
300	30	13.5	0.42	0.16	9.4	7.6	143	4.8	105.0	
	Recovery									
	31	14.4	0.45	0.19	9.4	6.6	145	4.4	107.9	
<b>0328</b>										

Addendum 5 -Continued  
Blood chemistry

B11-0301

	Exp. group (mg/kg/day)	Animal No. (#g/dl)	BUN (mg/dl)	Creatinine (mg/dl)	T-Bil (mg/dl)	Ca (mg/dl)	IP (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
Sex										
	37	11.5	0.34	0.28	9.6	8.4	14.2	4.7	106.9	
	38	14.0	0.42	0.27	9.7	8.3	14.3	4.6	105.3	
	39	16.0	0.38	0.26	9.8	8.8	14.3	4.6	104.5	
	40	16.0	0.41	0.25	10.0	7.9	14.4	4.6	106.3	
	41	14.3	0.37	0.24	9.5	8.1	14.5	4.4	106.8	
	42	14.5	0.48	0.17	10.1	8.6	14.6	4.3	106.4	
Hale										
	Recovery									
	4.3	16.7	0.51	0.16	9.5	7.8	14.3	4.5	108.3	
	4.4	15.0	0.42	0.18	9.7	7.5	14.2	4.0	106.2	
	4.5	17.0	0.49	0.18	9.2	7.2	14.3	4.4	108.5	
	4.6	14.2	0.44	0.23	9.6	7.3	14.2	4.5	103.7	
	4.7	15.6	0.51	0.17	9.7	7.4	14.4	4.2	106.1	
	4.8	12.8	0.43	0.19	9.6	7.6	14.2	4.9	108.1	

0329



Addendum 5 -Continued  
Blood chemistry

Sex	Exp. group (mg/kg/day)	BUN (mg/dl)	Creatinine (mg/dl)	T-Bil (mg/dl)	Ca (mg/dl)	IP (mg/dl)	Na (mEq/l)	K (mEq/l)	C1 (mEq/l)
	85	13.3	0.42	0.18	9.6	7.6	14.5	4.4	106.6
	86	17.0	0.39	0.22	9.2	7.9	14.5	4.4	108.5
	87	12.9	0.45	0.17	10.2	8.0	14.1	4.1	106.2
	88	12.9	0.37	0.22	9.7	7.8	14.3	4.5	107.8
	89	13.8	0.36	0.23	9.8	7.8	14.1	4.6	106.1
	90	12.1	0.35	0.21	10.0	8.0	14.1	4.6	105.6
<hr/>									
Female									
	Recovery	13.6	0.47	0.20	9.5	6.0	14.1	5.2	109.1
	91	14.2	0.50	0.17	9.4	6.3	14.2	4.7	110.5
	92	15.5	0.54	0.15	9.5	6.8	14.0	4.9	104.3
	93	14.8	0.47	0.16	10.1	6.5	14.1	4.5	108.7
	94	15.5	0.50	0.19	10.0	8.0	14.1	4.4	108.8
	95	15.2	0.43	0.17	10.1	6.2	14.3	4.3	112.0
	96								

0331

Addendum 6    28-day repeated-dose oral toxicity study in rats  
Urinalysis

Sex	Exp. group (mg/kg/day)	Animal No.	Volume (ml)	Color	pH	Protein	Ketones	Bilirubin	Occult Blood	Glucose	Urobilinogen (EU/dl)
		1	26	SY	7.0	±	±	-	-	-	0.1
		2	13	SY	6.5	+	±	-	-	-	0.1
		3	14	SY	6.5	±	±	-	-	-	0.1
		4	37	SY	7.0	+	±	-	-	-	0.1
		5	11	Y	6.5	+	±	-	-	-	0.1
		6	11	Y	7.0	+	±	-	-	-	0.1
Vehicle control											
		Recovery									
		7	13	SY	7.0	±	±	-	-	-	0.1
		8	18	SY	7.0	±	±	-	-	-	0.1
		9	6	Y	6.5	++	±	-	-	-	1
		10	10	B	7.0	++	±	-	+	-	1
		11	7	Y	6.5	++	±	-	-	-	0.1
		12	7	Y	6.5	++	±	-	-	-	0.1
Male											
		13	12	Y	7.0	+	±	-	-	-	0.1
		14	7	Y	6.5	++	±	-	-	-	1
		15	10	Y	7.0	+	±	-	-	-	0.1
		16	5	Y	6.5	++	±	-	-	-	1
		17	12	SY	7.0	+	±	-	+	-	0.1
		18	10	Y	6.5	+	±	-	-	-	0.1
		19	18	SY	7.0	±	±	-	-	-	0.1
		20	17	SY	6.5	+	±	-	-	-	0.1
40		21	10	Y	6.5	+	±	-	-	-	0.1
		22	17	SY	6.5	±	±	-	-	-	0.1
		23	29	SY	7.0	±	±	-	-	-	0.1
		24	14	SY	6.5	±	±	-	-	-	0.1

SY : Slightly yellow  
Y : Yellow  
B : Brown

0332

Addendum 6 — Continued  
Urinalysis

Sex	Exp. group (mg/kg/day)	Animal No.	Volume (ml)	Color	pH	Protein	Ketones	Bilirubin	Occult Blood	Glucose	Urobilinogen (EU/dl)
	25	9	Y	6.5	+	±	-	-	-	-	0.1
	26	20	SV	6.5	±	±	-	-	-	-	0.1
	27	10	Y	6.5	±	±	-	-	-	-	0.1
	28	20	SV	6.5	±	+	-	-	-	-	0.1
	29	20	SV	6.5	±	±	-	-	-	-	0.1
	30	15	SV	7.0	±	±	-	-	-	-	0.1
200	Recovery										
	31	16	SV	7.0	±	±	-	-	-	-	0.1
	32	15	SV	6.5	±	±	-	-	-	-	0.1
	33	6	Y	6.5	++	±	++	-	-	-	1
	34	11	Y	6.5	+	±	-	-	-	-	0.1
	35	14	SV	7.0	±	±	-	-	-	-	0.1
	36	21	SV	7.0	±	±	-	-	-	-	0.1
Male											
	37	23	SV	7.0	±	±	-	-	-	-	0.1
	38	19	SV	7.0	±	±	-	-	-	-	0.1
	39	6	Y	5.0	++	±	-	-	-	-	1
	40	15	SV	7.0	±	±	-	-	-	-	0.1
	41	15	SV	6.5	±	±	-	-	-	-	0.1
	42	13	SV	6.5	±	±	-	-	-	-	0.1
1,000	Recovery										
	43	13	SV	6.5	+	±	-	-	-	-	0.1
	44	31	SV	6.5	±	±	-	-	-	-	0.1
	45	5	Y	6.0	++	±	-	-	-	-	1
	46	11	SV	6.5	+	±	-	-	-	-	0.1
	47	7	Y	6.5	+	±	-	-	-	-	1
	48	9	Y	6.5	+	±	-	-	-	-	0.1

SV: Slightly yellow  
Y: Yellow

0333

Addendum 6 — Continued  
Urinalysis

Sex	Exp. group (mg/kg/day)	Animal No.	Volume (ml)	Color	pH	Protein	Ketones	Bilirubin	Occult Blood	Glucose	Urobilinogen (EU/dl)
		49	11	SY	6.5	±	—	—	—	—	0.1
		50	11	SY	6.5	±	—	—	—	—	0.1
		51	18	SY	7.0	±	—	—	—	—	0.1
		52	18	SY	6.5	±	—	—	—	—	0.1
		53	10	Y	6.5	±	—	—	—	—	0.1
		54	20	SY	6.5	±	—	—	±	—	0.1
Vehicle control											
		Recovery	13	SY	6.5	±	—	—	—	—	0.1
		55	8	Y	6.5	±	—	—	—	—	0.1
		56	15	SY	7.0	±	—	—	—	—	0.1
		57	5	Y	6.5	++	—	—	—	—	1
		58	6	Y	6.5	+	—	—	—	—	1
		59	12	SY	6.5	±	—	—	—	—	0.1
Female											
		60	18	SY	7.0	±	—	—	—	—	0.1
		61	23	SY	6.5	±	—	—	—	—	0.1
		62	12	SY	6.5	±	—	—	—	—	0.1
	8	63	11	SY	6.5	±	—	—	—	—	0.1
		64	5	Y	6.5	+	—	—	—	—	0.1
		65	20	SY	7.0	±	—	—	—	—	0.1
		66	14	SY	6.5	±	—	—	—	—	0.1
		67	13	SY	6.5	±	—	—	—	—	0.1
		68	12	SY	6.5	±	—	—	—	—	0.1
40		69	5	Y	6.5	++	—	—	—	—	1
		70	12	SY	6.5	±	—	—	—	—	0.1
		71	7	Y	7.0	±	—	—	—	—	0.1
		72	—	—	—	—	—	—	—	—	—

SY : Slightly yellow  
Y : Yellow

0334

Addendum 6 — Continued  
Urinalysis

Sex	Exp group (mg/kg/day)	Animal No.	Volume (ml)	Color	pH	Protein	Ketones	Bilirubin	Occult Blood	Glucose	Urobilinogen (EU/dl)
		73	8	Y	6.5	±	-	-	-	-	0.1
		74	18	SY	7.0	±	-	-	-	-	0.1
		75	5	Y	6.5	++	-	-	-	-	1
		76	8	Y	6.5	±	-	-	-	-	0.1
		77	9	Y	6.5	±	-	-	-	-	0.1
		78	15	SY	6.5	±	-	-	-	-	0.1
200											
Recovery											
		79	7	Y	6.5	+	-	-	-	-	0.1
		80	12	SY	6.5	+	-	-	-	-	0.1
		81	18	SY	6.5	-	-	-	-	-	0.1
		82	5	Y	6.5	+	-	-	-	-	1
		83	9	Y	6.5	±	-	-	-	-	0.1
		84	15	SY	6.5	±	-	-	-	-	0.1
Female											
		85	17	SY	7.0	±	-	-	-	-	0.1
		86	5	YB	6.5	++	-	-	-	-	1
		87	11	SY	7.0	±	-	-	-	-	0.1
		88	23	SY	6.5	±	-	-	-	-	0.1
		89	8	Y	6.5	+	-	-	-	-	0.1
		90	8	Y	6.5	±	-	-	-	-	0.1
1,000											
Recovery											
		91	14	SY	7.0	±	-	-	-	-	0.1
		92	16	SY	7.0	±	-	-	-	-	0.1
		93	8	Y	6.5	±	-	-	-	-	0.1
		94	4	Y	6.0	++	-	-	-	-	1
		95	15	SY	6.5	±	-	-	-	-	0.1
		96	8	Y	6.5	+	-	-	-	-	0.1

SY: Slightly yellow  
Y: Yellow  
YB: Yellow brown

00335



Addendum 7 -Continued  
Absolute organ weights

Sex	Exp.-group ( $\mu$ g/kg/day)	Animal No.	Spleen (g)	Liver (g)	Kidney (g)	Brain (g)	Testis (g)	Adrenal gland ( $\mu$ g)	Ovary ( $\mu$ g)	Body weight (g)
	37	0.45	10.81	2.52	2.00	2.54	4.17	-	288.6	
	38	0.66	11.34	2.21	1.87	2.42	37.5	-	300.3	
	39	0.57	11.75	2.46	1.78	2.72	45.8	-	298.8	
	40	0.69	12.18	2.75	1.84	2.68	50.4	-	315.6	
	41	0.51	10.61	2.32	1.81	2.67	45.4	-	283.2	
	1,000	42	0.52	11.18	2.38	1.83	2.51	39.1	-	293.8
<hr/>										
Male										
	Recovery	43	0.91	11.40	2.67	2.00	3.03	53.0	-	376.1
		44	0.72	11.10	2.63	1.95	2.64	44.4	-	364.9
		45	0.64	9.32	2.35	1.98	2.70	54.9	-	327.7
		46	0.75	11.60	2.98	1.97	3.18	53.5	-	396.8
		47	0.57	10.33	2.54	1.99	2.57	48.5	-	346.8
		48	0.76	10.50	2.68	1.93	2.71	60.5	-	340.1

0337



Addendum 7 -Continued  
Absolute organ weights

Sex	Exp. group (mg/kg/day)	Animal No.	Spleen (g)	Liver (g)	Kidney (g)	Brain (g)	Testis (g)	Adrenal gland (mg)	Ovary (mg)	Body weight (g)
	85	0.46	8.46	1.68	1.95	-	-	59.0	83.8	210.7
	86	0.45	7.41	1.44	1.88	-	-	57.8	97.3	176.1
	87	0.36	8.12	1.84	1.76	-	-	65.4	81.2	186.2
	88	0.46	9.40	1.81	1.85	-	-	62.2	96.1	215.6
	89	0.48	8.69	1.83	1.79	-	-	56.1	93.2	206.8
	90	0.35	7.96	1.63	1.70	-	-	55.7	67.3	184.4
<hr/>										
Female										
		Recovery								
	91	0.53	6.51	1.85	1.79	-	-	55.0	93.6	224.7
	92	0.51	7.62	1.76	1.79	-	-	75.2	95.8	243.4
	93	0.48	7.45	1.82	1.82	-	-	58.3	123.2	228.7
	94	0.47	7.75	1.71	1.89	-	-	65.2	109.5	238.6
	95	0.51	6.27	1.56	1.81	-	-	59.8	89.6	216.2
	96	0.56	7.70	1.93	1.95	-	-	78.1	87.1	252.0

0339



Addendum 8 -Continued  
Relative organ weights

Sex	Exp. group ( $\mu$ g/kg/day)	Animal No.	Spleen (g/100g)	Liver (g/100g)	Kidney (g/100g)	Brain (g/100g)	Testis (g/100g)	Adrenal gland ( $\mu$ g/100g)	Ovary ( $\mu$ g/100g)	Body weight (g)
Male	3,777	37	0.16	3.75	0.87	0.69	0.88	14.4	-	288.6
	3,888	38	0.22	3.78	0.74	0.62	0.81	12.5	-	300.3
	3,939	39	0.19	3.93	0.82	0.60	0.91	15.3	-	298.8
	4,040	40	0.22	3.85	0.87	0.58	0.85	16.0	-	315.6
	4,141	41	0.18	3.75	0.82	0.64	0.94	16.0	-	283.2
	4,242	42	0.18	3.81	0.81	0.62	0.85	13.3	-	293.8
	<hr/>									
	Recovery	4.3	0.24	3.03	0.71	0.53	0.81	14.1	-	376.1
	4.4	44	0.20	3.04	0.72	0.53	0.72	12.2	-	364.9
	4.5	45	0.20	2.84	0.72	0.60	0.82	16.8	-	327.7
	4.6	46	0.19	2.92	0.75	0.50	0.80	13.5	-	396.8
	4.7	47	0.16	2.98	0.73	0.57	0.74	14.0	-	346.8
	4.8	48	0.22	3.09	0.79	0.57	0.80	17.8	-	340.1

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Addendum 8 -Continued  
 Relative organ weights

B11-0301

Sex	Exp. group (mg/kg/day)	Animal No.	Spleen (g/100g)	Liver (g/100g)	Kidney (g/100g)	Brain (g/100g)	Testis (g/100g)	Adrenal gland (mg/100g)	Ovary (mg/100g)	Body weight (g)
Vehicle control	49	0.22	2.84	0.82	0.81	—	—	24.4	42.7	208.5
	50	0.17	3.14	0.85	0.89	—	—	28.7	35.7	200.3
	51	0.20	3.17	0.77	0.90	—	—	27.5	43.3	202.8
	52	0.19	3.06	0.76	0.91	—	—	28.3	39.9	201.1
	53	0.22	3.26	0.86	0.90	—	—	27.4	34.5	199.4
	54	0.21	3.36	0.85	0.82	—	—	33.9	49.9	205.4
	Recovery	55	0.24	2.72	0.70	0.78	—	—	—	—
	56	0.20	2.80	0.75	0.86	—	—	28.0	46.5	212.1
	57	0.15	2.57	0.68	0.86	—	—	26.8	43.8	207.7
	58	0.20	2.75	0.75	0.82	—	—	27.7	39.6	224.5
8	59	0.17	2.90	0.81	0.83	—	—	29.6	36.6	218.0
	60	0.22	2.86	0.72	0.78	—	—	27.4	40.5	242.6
	61	0.28	3.14	0.75	0.85	—	—	29.6	43.1	192.5
	62	0.21	2.83	0.82	0.93	—	—	24.5	35.2	183.8
	63	0.19	2.98	0.78	0.89	—	—	30.4	46.5	181.5
	64	0.24	3.23	0.83	0.88	—	—	30.4	38.8	208.7
	65	0.20	3.29	0.88	0.97	—	—	33.9	49.8	185.4
	66	0.20	3.01	0.78	0.90	—	—	29.9	35.1	198.9
40	67	0.17	2.84	0.71	0.89	—	—	24.9	38.9	183.5
	68	0.22	3.04	0.80	0.97	—	—	25.6	38.7	170.6
	69	0.20	3.16	0.91	0.90	—	—	35.7	43.2	189.6
	70	0.24	3.67	0.92	0.92	—	—	33.6	45.5	199.2
	71	0.24	3.26	0.83	0.95	—	—	27.4	39.3	182.5
	72	0.23	2.97	0.82	0.84	—	—	24.0	37.9	217.4
	73	0.25	3.45	0.93	0.94	—	—	26.7	30.7	192.8
	74	0.16	3.51	0.91	0.87	—	—	27.9	38.8	182.2
200	75	0.28	3.40	0.85	0.90	—	—	27.4	46.5	193.9
	76	0.22	3.75	0.79	0.90	—	—	31.5	45.4	196.9
	77	0.25	3.49	0.92	0.96	—	—	35.3	38.2	195.3
	78	0.23	3.24	0.85	0.92	—	—	32.5	43.8	202.0
	Recovery	79	0.18	2.83	0.82	0.82	—	—	—	—
	80	0.22	2.79	0.80	0.82	—	—	24.5	36.6	217.8
	81	0.22	3.52	0.93	0.78	—	—	33.1	40.2	233.8
	82	0.18	3.04	0.76	0.84	—	—	31.5	47.4	213.5
1	83	0.18	2.88	0.80	0.79	—	—	29.2	39.4	232.2
	84	0.16	3.21	0.83	0.73	—	—	26.0	40.1	249.2

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Addendum 8 -Continued  
Relative organ weights

Sex	Exp. group (ug/kg/day)	Animal No.	Spleen (g/100g)	Liver (g/100g)	Kidney (g/100g)	Brain (g/100g)	Testis (g/100g)	Adrenal gland (ug/100g)	Ovary (ug/100g)	Body weight (g)
Female	1,000	85	0.22	4.02	0.80	0.83	-	28.0	39.8	210.7
		86	0.26	4.21	0.82	1.07	-	32.8	55.3	176.1
		87	0.19	4.36	0.99	0.95	-	35.1	43.6	186.2
		88	0.21	4.36	0.84	0.86	-	28.8	44.6	215.6
		89	0.23	4.20	0.88	0.87	-	26.6	45.1	206.8
		90	0.18	4.32	0.88	0.92	-	30.2	36.5	184.4
		Recovery	0.24	2.90	0.82	0.80	-	24.5	41.7	224.7
		91	0.21	3.13	0.72	0.74	-	30.9	39.4	243.4
		92	0.21	3.26	0.80	0.80	-	25.5	53.9	228.7
		93	0.21	3.20	0.72	0.79	-	27.3	45.9	238.6
		94	0.24	2.90	0.72	0.84	-	27.7	41.4	216.2
		95	0.22	3.06	0.77	0.77	-	31.0	34.6	252.0
		96	0.22	3.06	0.77	0.77	-			

0343

Addendum 9 28-day repeated-dose oral toxicity study in rats  
 Pathological findings

[ B11-0301 ]

Sex	Exp. group (mg/kg/day)	Animal No.	Fate	Gross findings	Histopathological findings
		1	ta	NAD	Liver Microgranuloma ±
		2	ta	NAD	Liver Microgranuloma ±
		3	ta	NAD	NAD
		4	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets +
		5	ta	NAD	NAD
		6	ta	NAD	Liver Perilobular lipid droplets ±
Vehicle control	Recovery group				
		7	ta	NAD	Liver Microgranuloma +
Male		8	ta	NAD	Liver Microgranuloma ± Kidney Cyst formation
		9	ta	NAD	NAD
		10	ta	NAD	Liver Microgranuloma ±
		11	ta	NAD	Liver Microgranuloma +
		12	ta	NAD	Liver Microgranuloma ±
		13	ta	Kidney Pelvic dilatation (right)	Kidney Pelvic dilatation
		14	ta	NAD	NAD
8		15	ta	NAD	NAD
		16	ta	NAD	NAD
		17	ta	NAD	NAD
		18	ta	NAD	NAD

ta, terminal autopsy.

NAD, no abnormalities detected.

±, very slight; +, slight; ++, moderate; +++, severe.

0344

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Addendum 9 -Continued  
Pathological findings

[B11-0301]

Sex	Exp. group (mg/kg/day)	Animal No.	Fate	Gross findings	Histopathological findings
40	19	ta	NAD		NAD
	20	ta	NAD		NAD
	21	ta	NAD		NAD
	22	ta	NAD		NAD
	23	ta	NAD		NAD
	24	ta	Kidney Pelvic dilatation (left)	Kidney Pelvic dilatation	Kidney Pelvic dilatation
Male	25	ta	Kidney Pelvic dilatation (right)	Liver Microgranuloma ± Kidney Pelvic dilatation	
	26	ta	NAD	Kidney Increased eosinophilic bodies +	
	27	ta	NAD	Liver Microgranuloma ± Kidney Increased eosinophilic bodies +	
	28	ta	NAD	Liver Microgranuloma ±	
	29	ta	NAD	Kidney Increased eosinophilic bodies +	
	30	ta	NAD	Liver Microgranuloma ±	
200	Recovery group				
	31	ta	NAD		NAD
	32	ta	NAD	Liver Microgranuloma +	
	33	ta	Kidney Pelvic dilatation (bilateral) Glandular stomach Blackish spot of mucosa	Liver Microgranuloma ± Kidney Pelvic dilatation Glandular stomach Necrosis of mucosa +	
	34	ta	NAD		NAD

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Addendum 9 -Continued  
Pathological findings

[ B11-0301 ]

Sex	Exp. group (mg/kg/day)	Animal No.	Fate	Gross findings	Histopathological findings
		35	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets ±
	200	36	ta	NAD	Liver Microgranuloma ±
		37	ta	Kidney Apparent spotty pattern of surface (bilateral)	Liver Swelling of hepatocytes + Kidney Increased eosinophilic bodies ++ Forestomach Mucosal degeneration ±
		38	ta	NAD	Liver Granulation tissue with calcification + Kidney Increased eosinophilic bodies + Forestomach Mucosal degeneration ±
Male	1,000	39	ta	Kidney Apparent spotty pattern of surface (bilateral) Glandular stomach Roughening of mucosa Skin Scab formation (neck)	Liver Swelling of hepatocytes + Kidney Increased eosinophilic bodies ++ Forestomach Mucosal degeneration + Glandular stomach NAD Skin Scab formation +
		40	ta	Kidney Apparent spotty pattern of surface (bilateral)	Liver Swelling of hepatocytes + Kidney Increased eosinophilic bodies +++
		41	ta	NAD	Kidney Increased eosinophilic bodies ++ Forestomach Mucosal degeneration ±
		42	ta	Kidney Apparent spotty pattern of surface (bilateral)	Kidney Increased eosinophilic bodies +++ Forestomach Mucosal degeneration ±

00346

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Addendum 9 -Continued  
 Pathological findings

[ B11-0301 ]

Sex	Exp. group (mg/kg/day)	Animal No.	Fate	Gross findings	Histopathological findings
Recovery group					
		43	ta	NAD	Liver Microgranuloma +
		44	ta	NAD	Liver Microgranuloma ±
		45	ta	NAD	Liver Microgranuloma ±
Male	1.000	46	ta	NAD	NAD
		47	ta	NAD	Liver Microgranuloma ± Kidney Increased eosinophilic bodies +
		48	ta	NAD	NAD

00347

Addendum 9 -Continued  
Pathological findings

[ B11-0301 ]

Sex	Exp. group (mg/kg/day)	Animal No.	Fate	Gross findings	Histopathological findings
		49	ta	NAD	Liver Microgranuloma +
		50	ta	NAD	Liver Microgranuloma ±
		51	ta	NAD	Liver Perilobular lipid droplets + Kidney Fibrosis +
		52	ta	NAD	Liver Microgranuloma + Perilobular lipid droplets +
		53	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets +
	Vehicle control	54	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets +
Female					
		Recovery group			
		55	ta	NAD	Liver Microgranuloma +
		56	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets +
		57	ta	NAD	Liver Microgranuloma +
		58	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets ±
		59	ta	NAD	NAD
		60	ta	NAD	Liver Microgranuloma + Perilobular lipid droplets ±
		61	ta	NAD	Not examined
		62	ta	NAD	Not examined
8		63	ta	NAD	Not examined
		64	ta	NAD	Not examined

0348

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Addendum 9 -Continued  
Pathological findings

[ B11-0301 ]

Sex	Exp. group (mg/kg/day)	Animal No.	Fate	Gross findings	Histopathological findings
8		65	ta	NAD	Not examined
		66	ta	NAD	Not examined
		67	ta	NAD	Liver Microgranuloma ±
40		68	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets +
		69	ta	NAD	NAD
		70	ta	NAD	Liver Microgranuloma +
		71	ta	NAD	Liver Microgranuloma ±
		72	ta	NAD	NAD
		73	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets +
Female		74	ta	NAD	Liver Microgranuloma ±
		75	ta	NAD	Liver Microgranuloma +
		76	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets ±
		200	77	ta	NAD
		77	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets +
		78	ta	NAD	NAD
		79	ta	NAD	Liver Microgranuloma ±
		80	ta	Kidney Rough surface (right)	Kidney Pelvic dilatation Pyelonephritis ++
		81	ta	NAD	Liver Perilobular lipid droplets ±

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Addendum 9 -Continued  
Pathological findings

B11-0301

Sex	Exp. group (mg/kg/day)	Animal No.	Fate	Gross findings	Histopathological findings
Male	200	82	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets ±
		83	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets +
		84	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets +
	1,000	85	ta	NAD	Liver Microgranuloma ±
		86	ta	NAD	Liver Microgranuloma ± Swelling of hepatocytes +
		87	ta	NAD	Liver Perilobular lipid droplets +
Female	1,000	88	ta	NAD	Liver Microgranuloma ± Swelling of hepatocytes +
		89	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets ± Swelling of hepatocytes +
		90	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets + Swelling of hepatocytes +
	Recovery group	91	ta	NAD	Liver Microgranuloma +
		92	ta	NAD	Liver Microgranuloma +
		93	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets +
		94	ta	NAD	Liver Microgranuloma ±
		95	ta	NAD	Liver Microgranuloma ± Perilobular lipid droplets ±

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Addendum 9 -Continued  
Pathological findings

[ B11-0301 ]

Sex	Exp. group (mg/kg/day)	Animal No.	Fate	Gross findings	Histopathological findings
Female	1,000	96	ta	NAD	Liver Microgranuloma + Perilobular lipid droplets ±

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